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DOCTOR OF PHILOSOPHY

Neuropsychological function as a result of chronic exposure to methadone and other opioids

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Alexander Baldacchino

2012

University of Dundee

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Neuropsychological function as a result of chronic exposure to methadone and other opioids.

Dr Alex Baldacchino MPhil, MD, FRCPsych.

Thesis submitted for the degree of Doctor of Philosophy, University of Dundee.

April 2012

Mind your thoughts, as they become words.
Mind your words, as they become actions.
Mind your actions, as they become habits.
Mind your habits, as they define character.
Mind your character, as it becomes destiny.

Yorùbá Proverb

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Declaration

I hereby certify that I, Alexander Mario Baldacchino, declare that I am the sole author of this thesis and that all of the references cited in this manuscript have been consulted by me. The work of which this thesis is a record was carried out by me and has not been submitted in any previous application for a higher degree.

Dr Alexander Mario Baldacchino

PhD candidate

20th April 2012

We hereby certify that the candidate has fulfilled the conditions of Ordinance and Regulations for the degree of PhD (Clinical Psychiatry) in the University of Dundee.

Professor Keith Matthews

PhD Supervisor

20th April 2012

Professor David Balfour

PhD Supervisor

20th April 2012

Summary

It is increasingly recognised that chronic exposure to opioids has been associated with neuropsychological impairment during both active use and following a period of abstinence. The overall objective of this thesis was to review the relevant prior literature in a systematic manner and subsequently to describe the effects of chronic exposure to prescribed and illicit opioids using an ambispective cohort study design.

A systematic literature review was conducted to identify if chronic (defined as a period for more than 3 months) exposure to opioids (prescribed and/or illicit) was associated with measurable neuropsychological deficits. This review was conducted accordingly to the Meta-analysis of Observational Studies in Epidemiology (MOOSE) and the Preferred Reporting Items for Systematic reviews and Meta-Analysis (PRISMA) guidelines. The results were subsequently described within three cognitive domains of intelligence, executive function and memory and learning. Out of a total of 905 articles extracted between 1964 and 2009, 49 articles were considered appropriate for selection and review.

Studies of current and abstinent chronic opioid users (illicit heroin users, patients prescribed methadone for illicit opioid dependence and patients taking opioids as part of the management of chronic pain) have identified performance deficits in measures of executive functioning and memory. These have included impairments within the domains of cognitive and motor impulsivity, strategic planning, cognitive flexibility, attention and memory. However other studies found no clear deficits when comparing the performance of healthy controls. The literature suggested that these neuropsychological deficits may be subject to at least partial recovery following initiation of methadone or total withdrawal from any opioids. This review also highlighted several methodological issues that affect the reliability, validity and clinical relevance of the results obtained.

Subsequently a two year ambispective cohort design study was conducted which tested representative opioid exposed participants and healthy controls. Cohorts of participants with validated histories of illicit heroin use (HEROIN, n=24), stabilised methadone maintenance (METHADONE, n=29), chronic opioid prescriptions for pain (CHRONIC PAIN, n=28) and controls (HEALTHY CONTROL, n=28) were recruited. The study was designed to test neuropsychological performance in the HEALTHY CONTROL and CHRONIC PAIN groups on one occasion; and for the HEROIN and METHADONE groups on three and two occasions respectively. The intention was to describe neuropsychological performance in the HEROIN group under conditions of stable illicit heroin use, in controlled opioid withdrawal and when subsequently stabilised on methadone. For the METHADONE group, participants were tested twice, six months apart, to test for changes induced by chronic exposure to methadone. Eligible, screened and consented individuals were tested on nine tests from the CANTAB test battery.

Data were analysed using univariate or repeated measures ANCOVA with a *between subjects factor* of GROUP. Further *a priori* subgroup analyses were conducted using (1) a two-group factor reflecting DEPENDENCE status and (2) a two-group factor reflecting INJECTING status separately as *between subject factors*. The homogeneity of variance across groups in repeated-measures design ANCOVAs was assessed by the *Mauchly Sphericity Test*. NART, age in years, SIMD, total Fagerström score, years in education and past alcohol use in years were used as covariates. A significance level of $p < 0.01$ was applied due to multiple testing, in addition to the *post-hoc Bonferroni* correction procedure.

On the Cambridge Gambling Task (CGT), HEROIN users placed higher bets earlier and risked more. They also showed increased motor impulsivity, impaired strategic planning and visuospatial memory on the Affective Go-NoGo (AGN), Stockings of Cambridge (SOC), and Delayed Matching to Sample (DMS) respectively.

METHADONE users deliberated longer and placed higher bets earlier on the CGT, but did not show a tendency to risk more. METHADONE users were also more inattentive and demonstrated poor strategic planning and visuospatial memory on the Spatial Span (SSP) task. The CHRONIC PAIN participants did not exhibit significant impairment in neuropsychological performance on all the CANTAB tasks. Participants from the HEROIN, METHADONE and CHRONIC PAIN groups did not present with impaired cognitive flexibility.

Chronic opioid dependence is associated with neuropsychological impairment reflected in altered performance on measures of risk taking and strategic planning. These data support the hypothesis that these neuropsychological impairments reflect an underlying trait vulnerability to drug taking and/or dependence rather than an effect of chronic exposure to opioids. Notably, motor impulsivity and visuospatial memory in HEROIN users improved after three weeks stability with methadone.

Methadone use seems to confer improvement in some aspects of neuropsychological performance following cessation of heroin and sustains other deficits during long term stable methadone treatment. Dependence and injecting status do not contribute to the causation or deterioration of the identified neuropsychological impairments.

Further long term longitudinal studies to help elucidate cognitive endophenotypes responsible for the components in the initiation, continuation and deterioration of neuropsychological deficits present in an opioid dependent population is necessary.

Abbreviations

α - alpha (type 1 error)

ANCOVA- analysis of covariance

ANOVA- analysis of variance

APA- American Psychiatric Association

β - beta (type 2 error)

BIS- Barrat Impulsiveness Scale

BSE- Between-Search Error

CANTAB- Cambridge Neuropsychological Test Automated Battery

CGT- Cambridge Gambling Task

CHC- Cattell-Horn-Carroll Theory

CIDI- Composite International Diagnostics Interview

CINA- Clinical Institute Narcotic Assessment Scale

COWS- Clinical Opiate Withdrawal Scale

CPR- Cardio Pulmonary Resuscitation

d - Cohen's d (effect size)

DL-PFC- Dorso-Lateral Prefrontal cortex

DMS- Delayed Matching to Sample task

DSE- Double Search Errors

DSM- Diagnostic and Statistical Manual of Mental Disorders

DTORS- Drug Treatment Outcome Research Study

DV-PFC- Dorso-Ventral Prefrontal cortex

EMIT- Enzyme Mediated Immunoassay

ELISA- Enzyme Linked Immunosorbant Assay

ϵ - Greenhouse- Geisser epsilon

EMBASE- Excerpta Medica dataBASE

EPHPP- Effective Public Health Practice Project

ES- Effect Size

Factor κ B- kappa-light-chain-enhancer of activated B cells

FAS- apoptosis antigen 1 (APO-1), or cluster of differentiation 95 (CD95) or tumor

necrosis factor receptor superfamily member 6 (TNFRSF6)

F- F ratio (Levene's test)
 FTQ- Fagerström Tolerance Questionnaire
 FTND- Fagerström Test for Nicotine Dependence
g- intelligence
Ga- auditory processing in intelligence
 GABA- γ -aminobutyric acid
Gc- crystallised Intelligence
 GC- Gas Chromatography
Gf- fluid intelligence
Gl/*r*- long term storage and retrieval
Gq- quantitative knowledge and intelligence
Grw- reading and writing and intelligence
Gs- processing speed in intelligence
Gsm- short term working memory
Gv- visual processing in intelligence
 gms- grams
 H- Kruskal-Wallis test statistics
 HRNB- Halstead-Reitan Neuropsychological Battery
 ICD-10/9- International Classification of Diseases 10/9th editions
 IED- Intradimensional/Extradimensional
 IGT- Iowa Gambling Task
 IQ- intelligence quotient
 ISD- Information Services Division (NHS Scotland)
 JNK3- C-Jun-N-terminal kinase 3
 K-S- Kolmogorov-Smirnov Test
 LC- Liquid Chromatography
*log*10- logarithmic data transformation
 LTM- Long Term Memory
 MAP-Maudsley Addiction Profile
 MDMA- ecstasy
 MINI- Mini International Neuropsychiatric Instrument

MMT- Methadone Maintenance Therapy

MOOSE- Meta-analysis Of Observational Studies in Epidemiology guidelines

mg- milligram

ms- milliseconds

μ receptors- mu receptors

n/N- number

NA- not available

NART- National Audit Reading Test

NDTMS- National Drug Treatment Monitoring System

NHS- National Health Service

NS- non-significant

NTORS- National Treatment Outcome Research Study

OCD- Obsessive Compulsive Disorder

OP- Opioid Peptide receptor family

p - probability (significance)

P-P- Probability-Probability

p38 - archetypal member of the second MAP Kinase (MAPK) -related pathway in

p53 - tumor suppressor protein that in humans is encoded by the *TP53* gene

mammalian cells

PAL- Paired Associate Learning

PET- Positron Emission Tomography

PFC- Prefrontal Cortex

PICO- Population, Interventions, Comparisons and Outcomes

PRISMA- Preferred Reporting Items for Systematic reviews and Meta-Analysis

PTAQ- Post Traumatic Amnesia Questionnaire

PTQ- Post Trauma Questionnaire

PTSD- Post Traumatic Stress Disorder

PubMed- database produced by the National Library of Medicine

PsychInfo- database produced by the American Psychological Association

OF-PFC- Orbito-Frontal Prefrontal Cortex

Q-Q- Quantile-Quantile

QUOROM- Quality of reporting of Meta-analysis
RGT- Risky Games Task
RT- reaction time
R:L- Right:Left Handedness
SCID-P- Structured Clinical Interview for DSM-III-R Patients
SD- standard deviation
SE- standard error
sec- second
SF-36- Short Form (36) Health Survey
sig - significant
sim- simultaneous
SIMD-Scottish Index of Multiple Deprivation
SPSS- Statistical Package for Social Sciences
SQRT- square root data transformation
SPT- Spatial Span Test
STM- Short Term Memory
STT- Subsequent Thinking Time
SOC- Stockings of Cambridge
SWM- Spatial Working Memory
TLC- Thin Layer Chromatography
TSE- Total Search Errors
U- Test statistics for the Mann Whitney Test
UK- United Kingdom
USA- United States of America
VAS- Visual Analogue Scale
vs- versus
VL-PFC- Ventro-Lateral Prefrontal cortex
VM-PFC- Ventro-Medial Prefrontal cortex
VTA- Ventral Tegmental Area
WAIS- Wescler Adult Intelligence Scale
WCST- Wisconsin Card Sorting Test

WHO- World Health Organisation

WSE- Within Search Error

χ^2 - Chi-squared test statistics

yrs- years

z scores- a data point expressed in standard deviation unit

CHAPTER 1: Introduction-Chronic effects of opioids on human neuropsychological functioning: a systematic and narrative review

This introductory Chapter will concentrate on addressing the question: What does the current literature tell us about the neuropsychological consequences of chronic opioid use if this was conducted as part of a systematic review?

Answers to this complex question were required in order to set the scene for an in-depth discussion in Chapter 2 on the methods used to plan an ambispective cohort study looking at the neuropsychological consequences of chronic heroin and methadone use in opioid dependent male individuals with subsequent experimental findings on these populations described in Chapters 3, 4, 5 and 6.

Introduction

Opiates (naturally occurring opioid receptor ligands, such as morphine and semi-synthetic ligands such as heroin) and opioids (synthetic ligands, such as fentanyl or methadone) have been associated with a number of neuropsychological impairments during both active use and after a period of abstinence (**Verdejo-Garcia *et al.*, 2007**).

A large body of studies have examined the acute, subacute and chronic effects of opioids using a wide variety of cognitive measures sensitive to component aspects of attention, memory, learning and executive functioning (**Chou *et al.*, 2003; Fernandez-Serrano *et al.*, 2010a; Ersche & Sahakian, 2007; Zacny, 1995; Miller, 1985**). However, the nature and extent of opioid-related impairments remains elusive. For instance, research on memory functions has resulted in a number of studies showing impairments in word/pattern recognition, learning and recall of words/figures, paired associate learning and retrieval (**Amir & Bahiri, 1994; Darke *et al.*, 2000, Ersche *et al.*, 2006a; Fishbein *et al.*, 2007a; Fishbein *et al.*, 2007b**). However, other studies did not find memory deficits in chronic, opioid dependent individuals (**Davis *et al.*, 2002; Mintzer *et al.*, 2005**). In addition to memory

function, studies on attention also showed mixed results. Studies either showed no impairments in attention (**Davis *et al.*, 2002; Soyka *et al.*, 2005**) or a significant reduction in attention span (**Specka *et al.*, 2000; Schindler *et al.*, 2004**).

Neuropsychological studies of chronic opioid users identified deficits in executive function measures. These have included impairments in cognitive flexibility (**Pirastu *et al.*, 2006**), in strategic planning (**Ersche *et al.*, 2006a; Ersche *et al.*, 2006b**), decision making (**Verdejo-Garcia *et al.*, 2007a; Verdejo-Garcia *et al.*, 2007b**) and inhibitory control (**Mintzer *et al.*, 2005**). However other studies found no clear deficits when comparing the performance of healthy controls, with that of opioid abstinent, polysubstance users, head injury patients or patients with chronic pain (**Rotterham-Fuller *et al.*, 2004; Tassain *et al.*, 2003**).

The accumulated literature tends to assume that neuropsychological function is commonly impaired as a consequence of chronic opioid use. It also specifically suggests that the impairments are different in chronic opioid use from those seen in acute and sub-acute users (**Zacny, 1995**).

This uncertainty of the effects of neuropsychological consequences directly attributable to chronic opioid use is partly due to the lack of synthesising the literature available in a consistent, objective and comprehensively as possible (**Verdejo-Garcia *et al.*, 2007b; Verdejo-Garcia *et al.*, 2007c**). Traditional literature reviews frequently summarise highly unrepresentative and biased samples of studies in an unsystematic and uncritical fashion (**Mulrow, 1994**).

Systematic reviews are literature reviews that adhere closely to a set of scientific methods that explicitly aim to limit systematic error (bias), mainly by attempting to identify, summarise, appraise and synthesis all relevant studies in order to answer a particular question (or set of questions) (**Petticrew & Roberts, 2007**). Intuitively systematic reviews are more 'fit for purpose' of answering specific questions and testing hypothesis than the traditional literature reviews (**Knipschild, 1994**;

Petticrew, 2001). Systematic reviews are less of a discussion of the literature and more of a scientific tool and therefore useful in when:

- There is uncertainty in the direction of effects of particular behaviour such as chronic opioid use
- There is a wide range of research on the subject but where the key questions remain unanswered such as questions on treatment, prevention, diagnosis or aetiology
- A general overall picture of the evidence in the topic area is needed to direct future research or policy efforts
- An accurate picture of past research and past methodological research is required to promote the development of new methodologies

This dissertation revisited the literature available using a robust systematic review process and then, based on the evidence synthesised, conducted a cohort study to identify, if any, neuropsychological deficits in chronic opioid dependent users.

Definitions

An opioid is described as either a natural derivative of opium or a synthetic substance with agonist (heroin and methadone), partial agonist (buprenorphine), or mixed agonist and antagonist activity at opioid receptors (**Trescot *et al.*, 2008**).

An opiate is described as either a natural derivative or a semi-synthetic constituent of opium (**Trescot *et al.*, 2008**).

Table 1.1: Opioid Classification.

Opioid Classification	Examples
Natural Agonist Opioids	Opium, morphine, codeine
Semi-synthetic Agonist Opioids	Heroin, oxycodone, hydrocodone, oxymorphone
Synthetic Agonist Opioids	Methadone, meperidine, fentanyl, tramadol
Mixed Antagonists (Partial Agonists)	Buprenorphine, nalbuphine, pentazocine
Antagonists	Naltrexone, naloxone, nalmifene

For the purpose of this thesis, the meanings of the terms 'opioid' and 'opiate' can be considered as largely synonymous, with 'opioid' being used, as it has a broader definition (**Sweetman, 2005**) (**Table 1.1**).

Opioid receptors are a group of G protein-coupled receptors with opioids acting as ligands (**Waldhoer *et al.*, 2004**). The endogenous opioids are dynorphins, enkephalins, endorphins, endomorphins and nociceptins. The opioid receptors are distributed widely in the brain but are also found in the spinal cord and digestive tract. There are four major subtypes of opioid peptide (OP) receptors; delta (δ) or OP₁, kappa (κ) or OP₂, mu (μ) or OP₃ and nociceptin or OP₄.

Acute opioid effects or intoxication with agonist opioids have euphorogenic, analgesic, sedative, and respiratory depressant effects (**Jaffe, 1990**). Intravenous injection of opioids present with a faster and stronger euphorogenic effect than if smoked or snorted. This is described by users as a 'rush' (**Leri, 2003**). Acute sensitisation of the opioid receptor develops in minutes during opioid use and abates in minutes to hours following the exposure to the opioid (**Leri, 2003**).

For the purpose of this thesis acute opioid intoxication will be considered as happening between 0-3 hours after exposure to the opioid.

Opioid withdrawal is defined as a maladaptive behavioural change, with physiological and cognitive concomitants that occur when blood or tissue concentrations of an opioid decline in an individual who had maintained prolonged heavy use of the opioid (**Department of Health, 2007**). Cessation of regular and frequent opioid use is associated with a dysphoric withdrawal syndrome. This withdrawal syndrome starts 6-8 hours after cessation of all opioids and is characterised by watering eyes, runny nose, yawning, sweating, restlessness, tremor, nausea, vomiting, diarrhoea, increased blood pressure and heart rate, chills, cramps and muscle aches, which can last 7–14 days (**Figure 1.1**) (**Jasinski, 1981; Jaffe, 1990**).

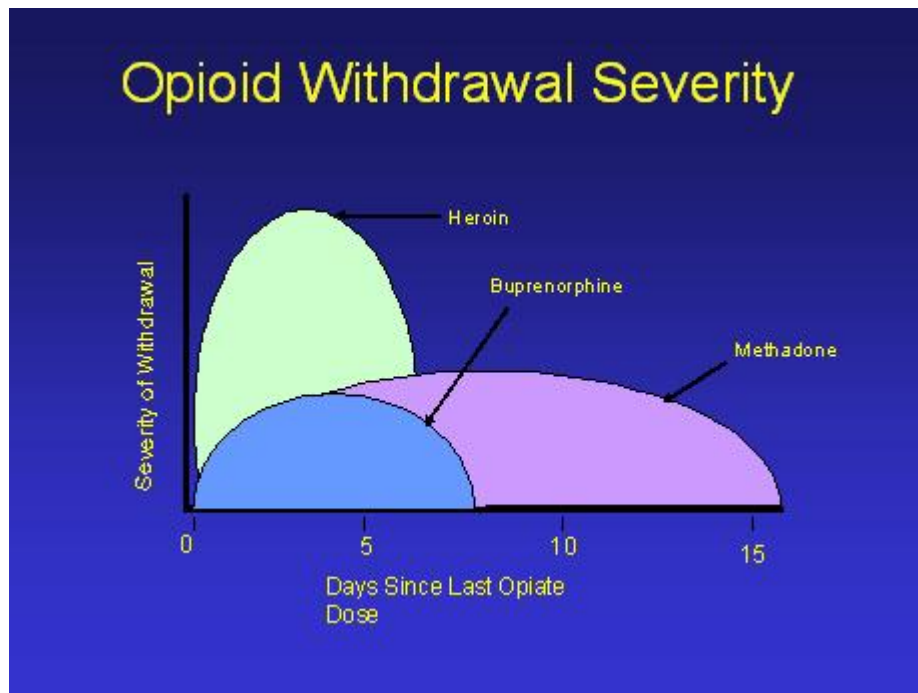


Figure 1.1: Opioid withdrawal for various types of opioids. Accessed from <http://www.addictionsurvivors.org/>. No permissions needed.

Subacute or post acute withdrawal opioid effects are effects that linger on for more than fourteen days, usually as prolonged withdrawal symptoms, and subside after three months from the last opioid use (Lejeune *et al.*, 1997). This protracted withdrawal can last months and can present with impaired cognition, insomnia, irritability, fatigue, drug craving, sweating, and dysphoria (Lejeune *et al.*, 1997). Symptoms occur intermittently and are not always present. Symptoms are made worse through stress or other triggers and may arise at unexpected times and for no apparent reason. An outline for conceptualizing protracted opioid withdrawal has been presented by Satel *et al.* (1993) in which these symptoms can be viewed as: (1) a global post acute syndrome, (2) attenuated opioid physiologic rebound, (3) opioid toxic residuals and (4) expression of pre-existing symptoms unmasked by cessation of use (Satel *et al.*, 1993).

For the purpose of this thesis subacute opioid effects include effects 1-3 months after the last use of opioid.

The term chronicity describes the repeated administration of opioid drugs with the adaptive mechanisms changing the functioning of opioid-sensitive neurons and neural networks perhaps in an irreversible manner (**Weiss *et al.*, 2001**). Adaptation is particularly a consequence of sustained mu receptor stimulation by opioid drugs (**Kieffer & Evans, 2002**).

Hallmarks of neuro-adaptations to chronic opioid use are:

- Tolerance, defined as a reduced sensitivity to the opioid effects and generally referring to attenuation of analgesic efficacy
- Drug craving
- Physiological manifestations of opioid withdrawal.

Adaptations following chronic opioid exposure extend well beyond reward circuits to other brain areas, notably those involved in learning and stress responses (**Koob, 2000**). Important regions affected are the amygdala, hippocampus and cerebral cortex and their connections to the nucleus accumbens. All these areas express opioid receptors and peptides, and the overall distribution of opioid peptide-expressing cells in neural circuits of dependence has been reviewed (**Nestler, 2001; Koob & Nestler, 1997**).

For the purpose of this thesis chronic use of opioids will indicate use of more than 3 months of daily and continuous opioid use.

Dependence is described as a cluster of cognitive, behavioural, and physiological symptoms indicating that the individual continues to use the substance despite significant substance related problems (**WHO, 1992**). All opioids have dependence potential to varying degrees (**Swadi *et al.*, 1990**). Of all the opioids, heroin has the greatest potential for dependency, especially when injected (**Martin & Jasinski, 1969; DH, 2007**). Physical and psychological dependence can develop within a relatively short period of continuous use (**NICE, 2007**). The World Health Organization (WHO) and the American Psychiatric Association (APA) state that the

key elements of opioid dependence are **(APA, 1994; WHO, UNODC and UNAIDS, 2006)**:

- A strong desire or sense of compulsion to take the substance
- Difficulty in controlling use
- A physiological withdrawal state
- Tolerance
- Neglect of alternative pleasures and interests
- Persistence of use despite harm to oneself and others

Cognition is defined as the process of knowing, including attending, remembering and reasoning as well as the content of these processes, such as concepts and memories **(WHO, 2004)**.

Neuropsychological deficits are defined as a reduction or impairment of cognitive function closely linked to the function of particular areas, neural pathways, or cortical networks in the brain. This term is particularly used when physical changes can be seen to have occurred in the brain, such as after neurological illness, mental illness, drug use, or brain injury **(Lezak, 1983; Lezak, 1984)**.

The term neurotoxic is used to describe a substance that damages the nervous system and/or brain, usually by destroying neurons **(Tilson, 1990)**. Structural neurotoxic effects are defined as neuroanatomical changes occurring at any level of nervous system organisation. Functional neurotoxic effects include adverse changes in somatic/autonomic, sensory, motor, and/or cognitive function. However the presence of neuropsychological deficits alone is not usually considered sufficient evidence of neurotoxicity, as many substances exist which may impair neuropsychological performance without resulting in the death or damage of neurons (behavioural toxicity) **(Albert, 1973)**. This may be due to the direct action of the substance, with the impairment and neuropsychological deficits being temporary, and resolving when the substance is metabolised from the body. In

some cases the level or exposure-time may be critical, with some substances only becoming neurotoxic in certain doses or time periods (**Tilson & Mitchell, 1983**).

Aim of the systematic review

The aim of this systematic review was to identify if chronic (> 3 months) exposure to opioids (prescribed and/or illicit) was associated with measurable neuropsychological deficits. If deficits were present what would the pattern of these deficits be? The review did NOT address treatment or prevention issues with regards to chronic opioid use and subsequent dependence.

Guidelines for data synthesis

This systematic review was conducted according to the Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines (**Stroup *et al.*, 2008**) and the Preferred Reporting Items for Systematic reviews and Meta-Analysis (PRISMA) guidelines (**Liberati *et al.*, 2009**).

Inclusion criteria

Articles selected satisfied the following criteria:

- Participants were aged over 18 years old
- International based literature studies on human cohort (i.e. not animal studies)
- All English and other articles written in any other language
- Chronicity of use and/or dependence to any opioids for more than three months
- Diagnosis of opioid dependence syndrome or abuse in the cohort studied (according DSM III/III-R/IV and/or ICD-9/ICD-10) (**APA, 1984; WHO, 1993**)
- Results reported separately for each neuropsychological task (i.e. not only composite scores)
- If several articles dealt with the same population the article with the largest sample size was selected

- Sufficient data available to calculate the effect (e.g. mean and standard deviation (SD), *F* statistics)
- If it was a follow up study, at least one month between test and re-test and with no specific training available to improve performance in the test used which might create practice effects

All different trials in order of decreasing internal validity (study design hierarchy) were included in this systematic review. These were grouped into (**Petticrew & Roberts, 2007**):

1. Experimental studies (e.g. Randomised Controlled Trials with concealed allocation)
2. Quasi-experimental studies (e.g. experimental study without randomisation)
3. Controlled observational studies divided into cohort studies and case controlled studies
4. Observational studies without control groups
5. Expert opinion based on pathophysiology, bench research or consensus

Search strategy and process

The literature search was carried out in two stages:

Stage 1: Literature search using electronic databases. The aim of this search was to provide an indication of the extent of available literature looking at the neuropsychological consequences of chronic opioid use between 1964 and December 2009 (45 years).

PubMed was the main database used to identify relevant literature. This database was selected because it provided access to over 15 million citations for biomedical and life sciences journals. The largest component of PubMed, Medline, provided access to citations from 1950 onwards. However, PubMed also provided access to

citations that have not been incorporated in Medline via a service of the National Library of Medicine (<http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?DB=pubmed>).

Project Cork database was selected to supplement citations identified through the PubMed search. Project Cork provided online access to 75,000 citations and literature on substance misuse for health professionals, educators, students and policy makers (<http://www.projectcork.org/>).

Social Science Citation Indices is a database of abstracts from some 2474 journals in the field of sociology and behavioural sciences included books, book chapters, dissertations and conference papers dating back to 1974 (http://thomsonreuters.com/products_services/science/science_products/a-z/social_sciences_citation_index/).

PsycINFO is a database produced by the American Psychological Association with a major emphasis on original research, while case studies, literature reviews, surveys and discussions are also covered. PsycINFO database provide extensive international coverage of the literature on psychology and allied fields from over 1,300 journals. Allied fields included information on drug and behavioural therapy, treatment of disease, drug addiction, developmental psychology, and educational psychology, as well as the psychological aspects of such areas as linguistics, social processes, pharmacology, physiology, nursing, education, anthropology, business and law dating back to 1887 (<http://www.apa.org/pubs/databases/psycinfo/index.aspx>).

The **Excerpta Medica database (EMBASE)**, produced by Elsevier, indexes over 3,500 international journals in the fields of pharmacology, pharmaceuticals, toxicology, clinical and experimental human medicine, health policy and management, public health, occupational health, environmental health, drug dependence and abuse, psychiatry, forensic medicine, and biomedical engineering. There was selective

coverage for nursing, dentistry, veterinary medicine, psychology, and alternative medicine (<http://www.embase.com/>).

Relevant articles were identified by using the following search strings by utilising a PICO (Population, Intervention, Comparisons and Outcomes) technique (**Booth & Fry-Smith, 2003**): '*chronic and/or repeated drug use/abuse/misuse/dependence/addiction and/or chronic opioid/opiate use/abuse/misuse/dependence/addiction AND neuropsychological deficits/impairments and/or neurocognitive deficits/impairments*'.

The term neuropsychological or neurocognitive was then replaced with a succession of terms describing the following neuropsychological tests ordered in standardised neuropsychological domains (**Lezak, 1984**).

(1) Intelligence and Aptitude Tests (**Anastasi & Urbina, 1997**).

- *National Adult Reading (NART)* (**Nelson, 1982**)
- *Raven's Progressive Matrices (RPM)* (**Raven, 1976; Raven, 1998**)
- *Shipley Institute to Living Scale* (**Shipley, 1940a**)
- *Shipley – Hartford Retreat Scale* (**Shipley, 1940b**)
- *Number Series Completion Test* (**Anderson, 1920**)
- *Wechsler Abbreviated Scale of Intelligence (WASI)* (**Psychological Corporation, 1999**)
- *Grammatical Reasoning Test (GRT)* (**Baddeley, 1968**)
- *Leistungs Pruf System (LPS)* (**Horn, 1962**)
- *Wechsler Test of Adult Reading (WTAR)* (**Lezak, 1983; Lezak, 1984**)

(2) Executive Function Tests (**Goldberg, 2001**) which included strategic planning, reasoning and cognitive flexibility.

- *Wisconsin Card Sorting Test (WCST)* (**Kongs et al., 2000**)
- *Porteus Mazes Test (PMT)* (**Porteus, 1933**)
- *Grooved Pegboard (GP)* (**Kløve, 1963**)

- *Minnesota Paper Forms Board Test (MPFBT)* (**Likert & Quasha, 1948**)
- *Tower of Hanoi and Tower of London (TOH and TOL)* (**Shallice, 1982**)
- *Logan Stop Change task (SCT)* (**Logan & Burkell, 1986**)

(3) Decision making which included risk taking and motor impulsivity tests.

- *Cambridge Risk Task or Rogers' Decision Making Task (RDMT)* (**Rogers et al., 1999b**)
- *Iowa Gambling Task (IGT)* (**Bechara et al., 1997**)
- *Barratt Impulsivity Scale (BIS)* (**Patton et al., 1995**)
- *Game and Dice Test (GDT)* (**Brand et al., 2002**)
- *Bechara Card Test (BCT)* (**Bechara et al., 1994**)
- *Delay Discounting Test (German DDT)* (**Forstmeier & Maercker, 2011**)

(4) Verbal Fluency Tests (**Goodglass & Kaplan, 1986**).

- *Benton Verbal Fluency Test (Benton VFT)* (**Benton et al., 1978**)
- *Controlled Oral Word Association Test and Phonological Fluency Test (COWAT/FAS)* (**Loonstra et al., 2001**)
- *Regensburger Word Fluency Test (RWFT)* (**Aschenbrenner, 2000**)
- *Ruff Figural Fluency Test (RFFT)* (**Ruff et al., 1987**)
- *Verbal Fluency Test (VFT)* (**Lezak, 1984**)

(5) Attention and Orientation Tests (**Parasuraman & Greenwood, 1998**).

- *Attention and Concentration Pauli Test* (**Arnold & Kohlmann, 1975**)
- *Paced Auditory Serial Addition Task (PASAT)* (**Gronwall, 1977**)
- *Test of Variables of Attention (TOVA)* (**Greenberg & Waldman, 1993**)
- *Test of Everyday Attention (TEA)* (**Robertson et al., 1994**)
- *Disturbed/Divided Attention Task (DAT)* (**Puglisi et al., 1988**)
- *Toulouse–Pieron's Concentration and Attention Test* (**Rainho, 1992**)
- *Knox Cube (Arthur Performance Test)* (**Richardson, 2005**)
- *Continuous Performance Test* (**Conners, 1992**)

- *Digit Symbol Substitution Test (DSST)* (**Lezak, 1995**)
- *Five Digit Test (5DT)* (**Sedo', 2005**)
- *Adult Memory and Information Processing Battery (AMIPB)* (**Vlaar & Wade, 2003**)
- *Visual Search Task (VST)* (**Schneider & Shiffrin, 1977**)
- *Stroop Word (Interference) Test (ST)* (**Golden , 1978**)
- *Farbe-Wort-Interferenz Test (FWIT)* (**Bäumler, 1985**)

(6) Reaction Time Tests (**Park et al., 1996**).

- *Continuous Reaction Time (CRT)* (**Bruhn & Parsons, 1971**)
- *Seriel Reaction Time (SRTT) and Simple Reaction Time (SRT)* (**Cleeremans & McClelland, 1991**)

(7) Verbal Memory Tests (**Gazzaniga et al., 2002**).

- *Verbal Memory (VM) Arnold Kohlmenn Tests* (**Arnold & Kohlmann, 1953**)
- *California Verbal Learning Test (CVLT)* (**Delis et al., 1990**)
- *Rey Auditory Verbal Learning Test (RAVLT) or Auditory Verbal Learning Test (AVLT)* (**Van Der Elst et al., 2005**)
- *Hopkins Verbal Learning Test (HVLt)* (**Benedict et al., 1998**)
- *Two-back Task (2BT)* (**Jaeggi et al., 2003**)
- *Digit Forward and Digits Backward Test (DFDBT)* (**Lezak, 1994**)
- *Word Recognition Memory (WRM)* (**Warrington, 1984**)

(8) Visuospatial Memory Tests (**Banich, 2004**).

- *Benton Visual Retention Test (BVRT)* (**Benton, 1974**)
- *Memory for Names and Faces (MNF)* (**Faw, 1990**)
- *Object Recognition Test (ORT)* (**Biederman, 1987**)

(9) Long Term Memory Tests **(Tulving, 1972).**

- *Story Recall and Recognition Test or Auditory Comprehension Test* **(Adejumo, 1980)**
- *Williams Delayed Recall Test (WDRT)* **(Williams, 1965)**
- *Rey Osterreith Complex Figure Test (RCFT)* **(Loring et al., 1990)**

(10) Other batteries of tests involving all or most of the above neuropsychological domains.

- *Act React Test Systems (ARTS and ART 2020)* which included Labyrinth of Lines to Measure Visual Structuring Performance (LL5), Simple Choice Reaction (DR2), Attention under Monotonous Circumstances (Q1), Tracking Test (CORT), Tachistoscopic Perception and Visual Orientation (TT15), Multiple Choice Reaction under Stress (RST3), Matrices Test for Intelligence (MAT/M30) and Test for Attention Flexibility (FAT) **(Bukasa et al., 1997).**
- *Bexley Maudsley Automated Psychological Screening* which included Spatial Little Men Test, Symbol Digit Test, Verbal Perceptual Analysis, Visuo-Spatial Recognition Memory and Bexley Maudsley Card Sorting Test (MCST) **(Acker & Acker, 1982)**
- *CANTAB Test* which included Pattern Recognition Memory (PRM) Task, Spatial Recognition Memory (SRM) Task, Attentional Set Shifting Task, Spatial Working Memory (SWM) Task, One Touch Tower of London Task, Tower of London (TOL), Visuo-spatial Strategy Task, Intra/Extra – Dimensional Set shifting Task (IED), Paired Associate Learning (PAL), , Cambridge Gambling Task (CGT), Continuous Performance Test (CPT), Information Sampling Task (IST) and Delayed Matching to Sample (DMS) Task **(Robbins et al., 1998; Sahakian et al., 1988)**
- *Halstead-Reitan Neuropsychological Test Battery* and its components such as Tactual Performance Test (TPT), Finger Tapping (FTT) or Oscillation Test, Rhythm Test, Trail Making Test (TMT) and Category Test **(Broshek & Jeffrey, 2000; Reitan, 1955)**

- *Weschler Adult Intelligence Scale-3rd Edition (WAIS III)* which included Pairs Associate Learning (PAL 1 +11), Letter Number Sequencing (LNC), Semantic and Phonological Fluency (FAS), Logical Memory Test (LMT), Digit Symbol and Visual Reproduction (VR 1 + 11), Verbal and Performance IQ (**Ryan & Lopez, 2001**)
- *Weschler Memory Scale Revised (WMSR)* which included Prose Recall Spatial Addition, Symbol Span, Design Memory, General Cognitive Screener, Logical Memory, Verbal Paired Associates, and Visual Reproduction (**Wechsler, 1945**)
- *Rivermead Behavioural Memory Test (RBMT)* (**Wilson et al., 1985**)
- *High Sensitivity Cognitive Screen (HSCT)* (**Faust & Fogel, 1989**)

Subsequently wild cards were also used including: 'addict*'; 'impair*'; 'drug*'; 'neuro*', 'medic*'.

Stage 2: Further literature search: This stage involved a more extensive collation of available literature identified through several sources and a preliminary review to inform the rationale for selection of articles. These included:

(A) Snowballing Technique: The reference list of the identified articles was then screened to find other studies on the subject.

(B) Hand Searching: Literature was further identified by hand searching the following 24 journals between 2003 and 2009.

- Mental Health/Psychiatry Journals: The American Journal of Psychiatry; Archives of General Psychiatry; British Journal of Psychiatry; Journal of Nervous and Mental Disease; Psychiatry Research; Psychological Medicine.

- Neuropsychology/Psychopharmacology Journals:

Psychopharmacology, Neuropsychology Review; Neuropsychopharmacology; Archives of Clinical Neuropsychology; Experimental and Clinical Psychopharmacology; Journal of Clinical Psychopharmacology; Journal of Psychopharmacology; Neuropsychologia; Human Psychopharmacology; Brain and Cognition; Neuroscience and Biobehavioral Review.

- Addiction Journals: Drug and Alcohol Dependence; Addictive Behaviours; Addiction; American Journal on Addictions; Drug and Alcohol Review; European Addiction Research.

- Pain Journals: Journal of Pain and Symptom Management; European Journal of Pain; Clinical Journal of Pain; Pain.

- General: The Lancet; Nature; British Medical Journal; Journal of American Medical Association.

(C) Experts in the field: Experts in the field of addiction and/or pain within various UK, European and other international academic and clinical centres were contacted for any relevant literature on neuropsychological consequences of chronic opioid use. They included centres in Norway, Denmark, Hungary, France, Spain, Italy, Malta, Poland, Bulgaria, Finland, Portugal, Germany, Greece and the United Kingdom (London, Keele, Glasgow, Stirling and Cambridge) from Europe and others from US and Australasia.

Data extraction and recording

Recorded variables

For the purpose of this review it was necessary to develop a strategy for analysing the selected literature. From each selected study, variables describing the methodology used such as definition of the case, study setting, population studied

and sampling methods used, criteria and recruitment processes, diagnostic or screening instruments and neuropsychological tests used and biological confirmatory tests for substance misuse were extracted. We also extracted variables describing the statistical analysis, type and strength of findings such as potential confounders and bias (**Table 1.2: Types of Bias**) together with ethical and other research governance components (**Appendix 1**).

Table 1.2: Types of bias.

Type	Description	Methods to minimise bias
Selection (allocation) bias	Systematic differences between comparison groups in prognosis or responsiveness to treatment	Randomisation of large numbers of patients Concealment of their allocation to different groups
Performance bias	Systematic differences in care provided apart from the intervention being evaluated	Standardisation of the care protocol and blinding of clinicians and participants
Measurement bias (detection bias, ascertainment bias)	Systematic differences between comparison groups in how outcomes were ascertained	Blinding of study participants and outcome assessors
Attrition bias (exclusion bias)	Systematic differences between comparison groups in terms of withdrawals or exclusions of participants from the study sample	Inclusion of such participants in the analysis (in combination with a sensitivity analysis)

Establishing valid neuropsychological constructs

In order to reliably group neuropsychological tests that provide similar results or have same concepts three workshops with leading neuropsychologists, health and clinical psychologists and neuropsychiatrists from Edinburgh, St Andrews and Stirling Universities were conducted. It was concluded that the ten neuropsychological domains described earlier in this chapter can be further collapsed into three broad domains as described by **Ersche *et al.*, (2007)** and **Potvin *et al.*, (2005)**. The neuropsychological tests and results in Chapters 4,5,6 were subsequently described using the following three domains:

(1) Intelligence (aptitude) neuropsychological domain.

(2) Executive Function neuropsychological domains which included:

- Cognitive impulsivity (reflection impulsivity and risk taking)
- Motor impulsivity (behavioural and cognitive inhibitions)
- Non-planning impulsivity or lack of strategic planning (reasoning and problem solving and central executive of working memory)
- Lack of cognitive flexibility or rigidity (reactive flexibility and spontaneous or verbal/non verbal fluency)
- Attention (arousal, focused and selective attention, sustained attention, resistance to interference, mental manipulation, reaction time, visual or iconic and auditory or echoic memory)

(3) Memory and learning neuropsychological domains which included:

- Attention as above
- Short term memory (immediate and working verbal or nonverbal or visuospatial)
- Long term memory (explicit or declarative or episodic or semantic and Implicit or non declarative or procedural or priming)

Intelligence (aptitude)

The Cattell-Horn-Carroll (CHC) theory of intelligence suggests that it is composed of a number of different abilities that interact and work together to produce overall individual intelligence (**McGrew, 1997; Wayne, 2003**). The CHC theory represents the integration of the Cattell-Horn 'Fluid Intelligence (Gf)-Crystallised Intelligence (Gc)' theory (**Horn & Noll, 1997; Horn & Cattell, 1967**) and Carroll's three-stratum theory (**Carroll, 1993, 1997**). This theory categorizes the intelligence function (g) according to the 10 overall cognitive factors:

- *Crystallised intelligence* or comprehension/knowledge intelligence (Gc) is a broad ability that involves an individual's breadth and depth of general and cultural knowledge, verbal communication and vocabulary, and ability to

reason using words and numbers with previously learned procedures. In other words what we have learned with language. This therefore improves with age. The Wechsler Adult Intelligence Scale- Revised (WAIS-R) measures crystallised intelligence on the verbal scale (**Weschler, 1981**).

- *Fluid intelligence* or reasoning intelligence (Gf) refers to mental operations used primarily when individuals are faced with tasks that cannot be performed automatically. In short it is defined as the ability to understand complex relationships and solve novel problems (**Martinez, 2000**) or logical thinking. Fluid reasoning is further subdivided into inductive reasoning and deductive reasoning. Cognitive tests that do not rely on acquired knowledge are viewed as good measures of fluid intelligence, such as Raven's Progressive Matrices (**Raven, 1998**), Cattell's Culture Fair Test (**Cattell, 1973**) and the performance subscale of the WAIS-R (**Weschler, 1981**). It also correlates well with measures of abstract reasoning and puzzle solving (**Ryan & Schnakenberg-Ott, 2003**).
- *Short-term working memory* (Gsm) is the ability to mentally hold information and then use this information within a few seconds (e.g. remembering a short message or a telephone number).
- *Long-term storage and retrieval* (Glr) refers to the ability to memorise information and to retrieve it.
- *Processing speed* (Gs) refers to the ability to quickly perform automatic, routine cognitive tasks.
- *Visual processing intelligence* (Gv) is the ability to perceive and remember visual input.
- *Auditory processing intelligence* (Ga) refers to the ability to analyse and synthesise auditory stimuli.
- *Others* such as quantitative knowledge (Gq) and reading and writing (Grw).

Researchers have been studying the relationship between working memory and fluid intelligence for more than a decade but still have not reached agreement on the precise relationship between working memory and fluid intelligence. Some have

argued that working memory is so highly correlated with fluid intelligence that they could be deemed isomorphic (Engle, 2002; Jensen, 1998; Kyllonen, 2002; Stauffer *et al.*, 1996), some have stated that these two constructs are barely linked to each other (Deary, 2000; Kline, 2000), while most have claimed that working memory and fluid intelligence are closely related but not identical (Ackerman *et al.*, 2005; Beier & Ackerman, 2005; Kane *et al.*, 2004).

It was agreed that this systematic review would group crystallised and fluid intelligence as core component of the general intelligence cognitive domain (Table 1.3), attention and processing speed as part of the decision making cognitive domain with the short term memory and long term storage and retrieval grouped within the learning and memory cognitive domains.

Table 1.3: Intelligence (aptitude).

Main Domain	Subtypes	Other names	Definition	Examples of test
Premorbid or Crystallised Intelligence	Verbal Intelligence Quotient (IQ)	Indicated by a person's depth and breadth of general knowledge, vocabulary, and the ability to reason using words and numbers	The ability to use skills, knowledge, and experience. It should not be equated with memory or knowledge, but it does rely on accessing information from long-term memory.	School Reports, NART, WAT, WAIS-III (Verbal), SILS, MWT-B, WTAR
General Intellectual Functioning or Fluid Intelligence	Performance Intelligence Quotient (IQ)	Fluid reasoning includes inductive and deductive reasoning	The capacity to think logically and solve problems in novel situations, independent of acquired knowledge. Ability to analyze novel problems, identify patterns and relationships that underpin these problems and the extrapolation of these using logic.	WAIS-III, (Performance), RPM, MMSE, WASI, SHRS, NSCT, SILS, LPS

LPS= Leistungs Prufsystem (German intelligence test battery), MMSE=Mini Mental State Examination, MWT-B= MehrfachwahlWortschatz-Intelligenz-Test (Multiple Choice Word Comprehension Test), NART=National Adult Reading Test, NSCT=Number Series Completion Test, RPM=Ravens Progressive Matrices, SHRS=Shipley–Hartford Retreat Scale, SILS=Shipley Institute to Living Scale, WAIS-III=Weschler Adult Intelligence Scale Third Edition, WASI=Wechler Abbreviated Scale of Intelligence, WAT= Word Accentuation Test, WTAR= Weschler Test of Adult Reading.

Executive Function

Modern concepts of executive functions are often traced to **Luria (1966)** who noted that patients with frontal-lobe damage frequently have their speech, motor abilities, and sensations intact yet are often unable to carry out complex, purposive, and goal directed actions. He also found that they could not accurately evaluate the success or failure of their behaviours and were unconcerned with their failures, and hesitant, indecisive, and indifferent to the loss of their critical self-awareness. **Lezak (1983)** also noted that frontal-lobe-damaged patients frequently lost their ability to be independent, constructive, creative, and socially productive and appropriate, despite their intact perceptual, language, and long term memory abilities.

Pennington & Ozonoff (1996) defined executive functions as a unique domain of abilities that involves 'organisation in space and time, selective inhibition, response preparation, goal-attainment, planning, and flexibility'. They viewed executive function as partially distinct yet overlapping with other neuropsychological domains such as sensation, perception, language, and long-term memory. Current neuropsychological assessment of executive function also invariably includes measures of planning, sequential memory, and temporal-order memory (**Lezak 1995**).

Impulsivity

The term impulsivity is used widely within psychology to refer to behaviour that is performed with little or inadequate forethought (**Evenden, 1999**). The term has a long history in the study of individual differences, as a trait variable of human personality that is stable within an individual and varies normatively across the healthy population (**Barratt, 1959; Patton et al., 1995**). Within neuropsychology and cognitive neuroscience, impulsivity is often equated with the term 'disinhibition', referring to the idea that top-down control mechanisms that ordinarily suppress automatic or reward-driven responses are not appropriate to the current demands (**Aron, 2007**). Impulsivity encompasses behaviours that are

rash, poorly planned, or focused on short-term outcomes despite potentially negative consequences in the long-term (**Ainslie, 1975; Dawe & Loxton, 2004**). It is a multiple component construct (**Lane *et al.*, 2003; Reynolds *et al.*, 2006**). For this thesis three constructs will be described: cognitive, motor and non-planning impulsivity.

(1) *Cognitive impulsivity* involves making quick cognitive decisions. The choices or decisions of more impulsive individuals are influenced by the immediately available outcomes despite their long-term consequences putting them in a position to sustain excessive long-term costs in exchange for modest short-term gains (**Baumeister & Scher, 1988; Cooper *et al.*, 2003; Kirby *et al.*, 1999**). Cognitive impulsivity may be related to psychometric constructs such as sensation seeking and urgency in **Whiteside & Lynam (2001)** and delay-discounting (**Ainslie, 1975; Mischel *et al.*, 1989, Bickel & Marsch, 2001; Reynolds, 2006**).

One element of cognitive impulsivity is 'reflection impulsivity', which refers to the tendency to gather and evaluate information before making complex decisions (**Kagan, 1966**). Inadequate reflection at the pre-decisional stage will reduce the accuracy of the eventual decision (**Evenden, 1999**). This is also known as decision-making under ambiguity when the outcomes are uncertain and the outcome probabilities are unknown or estimated (**Ernst & Paulus, 2005; Hastie, 2001**).

The Iowa Gambling Task (IGT) (**Bechara *et al.*, 1994**) is the most frequently used test to assess decisions under ambiguity. Other neuropsychological tests measuring reflection impulsivity include the Matching Familiar Figures Test (MFFT) (**Kagan, 1966**) and the Information Sampling Test (**Clark *et al.*, 2006**),

Cognitive impulsivity may also contribute to abnormal decision-making on tasks where the subject may select between a conservative option and a more risky option that offers a 'superficially seductive' gain (**Bechara & Martin, 2004; Knoch & Fehr, 2007**). This is also known as decision making under risk where the outcomes are uncertain but the outcome probabilities are known (**Camerer & Weber, 1992**).

Some tests used to measure risk taking include the Risky Gains Procedure (**Paulus et al., 2003**); Games of Dice Test (GDT) (**Brand et al., 2005; Brand et al., 2002**); Risky Gains Task (RGT) and Cambridge Gambling Task (CGT) (**Rogers et al., 1999a; Rogers et al., 1999b**) with the latter designed to investigate decision-making independently from learning. The last half of the IGT is thought to test both ambiguous and risky decision-making, so successful performance on this task is thought to require integrity of both the ventromedial and dorsolateral prefrontal brain areas (**Bechara et al., 1994; Clark et al., 2006**).

(2) *Motor Impulsivity (Response Inhibitory Control)* (**Olmstead, 2006; Barratt, 1985; Logan, 1994; Newman et al., 1987**). It involves acting without thinking and when individuals have difficulty in suppressing reward-driven automatic behaviour or prepotent responses (**Logan et al., 1997**). Inhibitory control can be investigated in both the behavioural (motor) and cognitive domains.

Behavioural (motor) response inhibition is defined as the process required to stop a planned movement (**Aron et al., 2004; Chamberlain & Sahakian, 2007**). Much of this work utilised **Logan's (1994)** Stop Signal Task and the Go/NoGo Task (**Newman et al., 1990**). Meanwhile cognitive inhibition is frequently assessed by the Stroop Test (**Stroop, 1992**), which requires participants to suppress a salient but conflicting stimulus property while identifying a less salient one (e.g., reading the word 'blue' that is written in red ink requires more cognitive effort, so-called interference control, than reading the word 'blue' when written in blue ink).

(3) *Non-Planning Impulsivity (Strategic Planning or Problem Solving)* is the ability to 'think ahead' and actively search for an appropriate solution (**Owen, 1997**). Lack of planning and forethought has also been considered a component of impulsive behaviour (**Dickman, 1990; Evenden, 1999**). Non-planning impulsivity is synonymous with lack of premeditation (**Whiteside & Lynam, 2001**).

Baddeley and others (**Baddeley & Logie, 1999; Miyake & Shah, 1999**) view working memory as orchestrated by an executive component (**Figure 1.2**) which involves attention, decision making, planning, sequencing, temporal tagging, and also helps update and integrate the information generated from the three 'slave systems' (phonological loop, visuospatial sketchpad and episodic buffer).

The Spatial Working Memory (SWM) Task and the Spatial Span Test (SST) from the CANTAB have been used to measure the executive aspect of working memory (**CANTAB**). This executive loop is considered as integral to non-planning impulsivity (**Baddeley & Logie, 1999; Baddeley, 2000**).

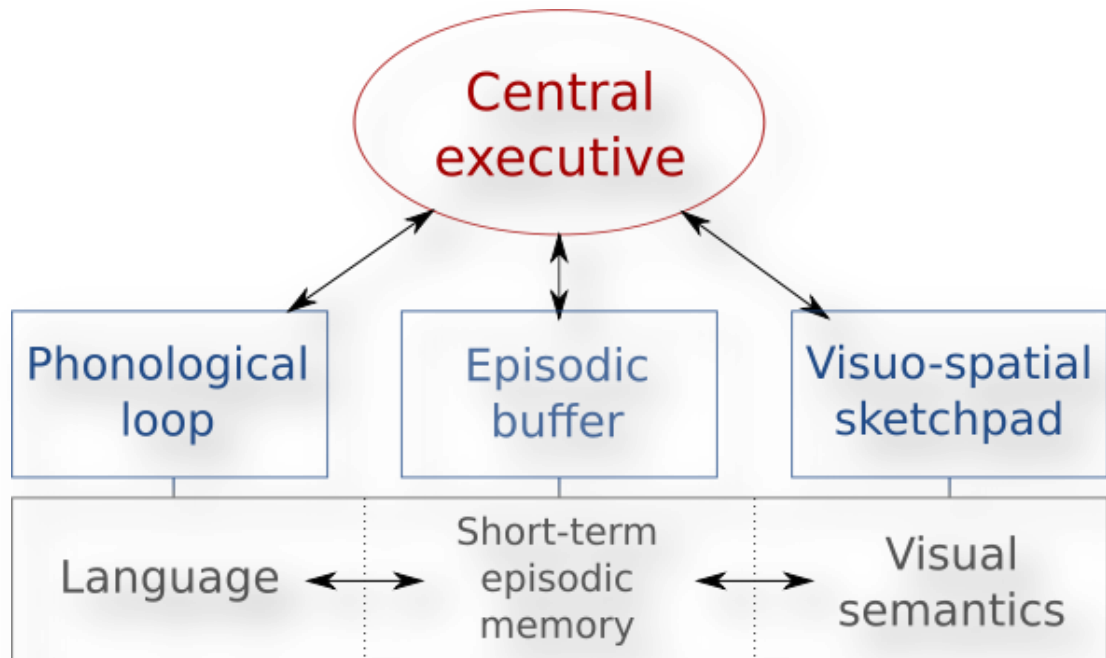


Figure 1.2: Revised Baddeley's working memory model (Baddeley, 2000).

Cognitive Flexibility

Cognitive flexibility has been defined as the ability for an individual to shift attention and to attend to environmental cues, and is considered as an important component in problem solving ability (**Lezak et al., 2004**). A lack of cognitive flexibility, or cognitive rigidity, appears to be a factor precluding individuals from discovering or employing alternative solutions to novel stimuli. **McGuire (2001)**

found that cognitive rigidity resulted in a lack of consideration of alternatives or consequences. Individuals tend to show difficulties in set shifting.

(1) *Reactive flexibility* is the ability to shift cognition or behavior in response to changing tasks or situational demands (perseveration). This shifting occurs when either external task conditions or self initiated decision require an alternative to the current response be chosen and executed. Different tasks and situations require different type of reactive shifts and presumably different underlying cognitive processes (**Grattan & Eslinger, 1989**). Reactive flexibility is assessed with the Intra/Extra-Dimensional Set Shifting (IED) Task, originally developed from the Wisconsin Card Sorting Test (WCST). This paradigm examines different components of attentional flexibility, including reversal learning (i.e. the ability to adapt behaviour after negative feedback) and the ability to inhibit and shift attention between stimulus dimensions (extra-dimensional shift) as observed in animal (**Dias et al., 1996**) and human (**Downes et al., 1989; Owen et al., 1991**) studies. To assess psychomotor speed and cognitive flexibility the Trail Making Test (TMT) (**Armitage, 1945**) is another tasks used. Trails Part A (TMT-A) is a more direct measure of psychomotor speed, whereas Trails Part B (TMT-B), with its set-switching demands, also reflects reactive flexibility (**Zinn et al., 2004**)

(2) *Spontaneous Flexibility (Fluency)* represents the ability to produce diverse ideas, consider response alternatives and modify plans. Verbal flexibility (verbal fluency) is often described as divergent thinking which emphasizes variety, quantity and relevance of information. Naming something quickly and accurately is an essential part of efficient spoken language (**Grattan & Eslinger, 1989**). This requires the rapid production of variations on a theme (words beginning with the same letter or line patterns connecting dots) while avoiding repetition. The Controlled Oral Word Association Test (COWAT) (**Borkowski et al., 1967; Loonstra et al., 2001**) assesses verbal fluency. The Ruff Figural Fluency Test (RFFT) (**Ruff et al. 1987, 1994**) assesses non-verbal fluency. Two subtests from the WAIS-III are used to assess concrete

thinking or lack of abstract reasoning which is another measure of cognitive flexibility (**Wechsler, 1997**).

Table 1.4 categorises the different components described in this chapter and grouped as executive function neuropsychological domain.

Table 1.4: Executive function.

Main Domain	Subtypes	Other names	Definition	Tests
Cognitive Impulsivity		Delay discounting or urgency	Ability to opt for larger delayed rewards over smaller more immediate rewards	
	(a) Reflection Impulsivity		Decision-making under ambiguity	IGT, MFFT, BIS, DDT
	(b) Risk taking		Decision-making under risk	CGT, IGT, , GDT
Motor Impulsivity		Inhibitory Control	Ability to suppress emotional, cognitive and behavioural responses	
	(a) Behavioural Inhibition	Motor Response Inhibition	Process requires to stop a planned movement	AGN, SS,,Go/NoGo
	(b) Cognitive Inhibition	Focused Attention	Process required to suppress a salient but conflicting stimulus while identifying less salient ones	ST
Non-planning Impulsivity	Reasoning and Problem Solving	Central Executive in working memory model Lack of pre-meditation	Ability to think ahead and actively search for an appropriate solution	TOL, SOC, ROCFT, PMT, TOH WAIS –III (Block Design, Matrix Reasoning), SSP, SWM
Cognitive Flexibility		Rigidity	Ability to shift avenues of thought and action in order to perceive process and respond to situations in different ways	
	(a) Reactive Flexibility	Perseveration or shifting of perceptual set	Ability to realign a behavioural predisposition to altered contingencies	WCST, ST, IED, TMT, SCT, MCST
	(b) Spontaneous Flexibility or fluency	Verbal and non verbal fluency	Requires the intrinsic generation of responses or alternatives	COWAT, FAS, VFT, RFFT, WAIS III (Similarities), RWT
Attention	(a) Deployment	(a) Arousal		Observation
		(b) Focused and Selected Attention	Ability to reject irrelevant information while attending to relevant input	WAIS –III (Digit Span), TMT, TEA, ST, AGN
		(c) Sustained Attention	Readiness to detect rarely and unpredictable occurring signals over prolonged periods of time	PASAT, TOVA, TEA, CFT
	(b)Capacity/Encoding or Data Processing		Ability for individuals to hold information in mind and process OR need to process tasks simultaneously	
		(a) Attention Span		CVLT, RAVLT
		(b) Reaction Time or information processing speed		DSST,WAIS (Digit Symbol)

AGN= Affective Go-NoGo (CANTAB), BIS= Barratt Impulsivity Scale, BLC= Big Little Circle, CGT= Cambridge Gambling Task (CANTAB), CFT= Continuous Performance Test, COWAT= Controlled Oral Word Association Test, CVLT= California Verbal Learning Test, DDT= Delay Discounting Test, DSST= Digit Symbol Substitution Test, FAS= Phonological Fluency Test, FFT= Finger Tapping Test, GDT= Game and Dice Test, IED= Intra/Extra-Dimensional Set Shifting Task (CANTAB), IST= Information Sampling Test, IGT= Iowa Gambling Task, MFFT= Matching Familiar Figures, MCST= Maudsley Card Sorting Test, PASAT= Paced Auditory Serial Addition Task, PMT= Proteus Maze Test, RAVLT= Rey Auditory Verbal Learning Test, ROCFT= Rey-Osterreith Complex Figure Test, RT= Reaction Time, RWT= Regensburg Word Fluency Test, SCT= Logan Stop Change Task, SOC= Stockings of Cambridge (CANTAB), SSP= Spatial Span (CANTAB), SS= Stop Signal, SWM= Spatial Working Memory (CANTAB), ST= Stroop Test, TEA= Test of Everyday Attention, TMT= Trail Making Test, TOH= Tower of Hanoi, TOL= Tower of London (CANTAB), TOVA= Test of Variables of Attention, VFT= Benton Verbal Fluency Test, WCST= Wisconsin Card Sorting Test, WAIS-III= Wechsler Adult Intelligence Scale Third Edition.

(3) Memory and Learning

To evaluate the effects of opioids, or any other drug, on memory and learning, one must first identify a model of memory formation and storage to use as a reference. One classic, often cited model, initially proposed by **Atkinson & Shiffrin (1968)**, described memory formation and storage as taking place in several stages, proceeding from sensory memory (which lasts up to a few seconds) to short-term memory (which lasts from seconds to minutes depending upon whether the information is rehearsed) to long-term memory storage. This model is often referred to as the Atkinson–Shiffrin Modal Model of Memory (**Figure 1.3**).

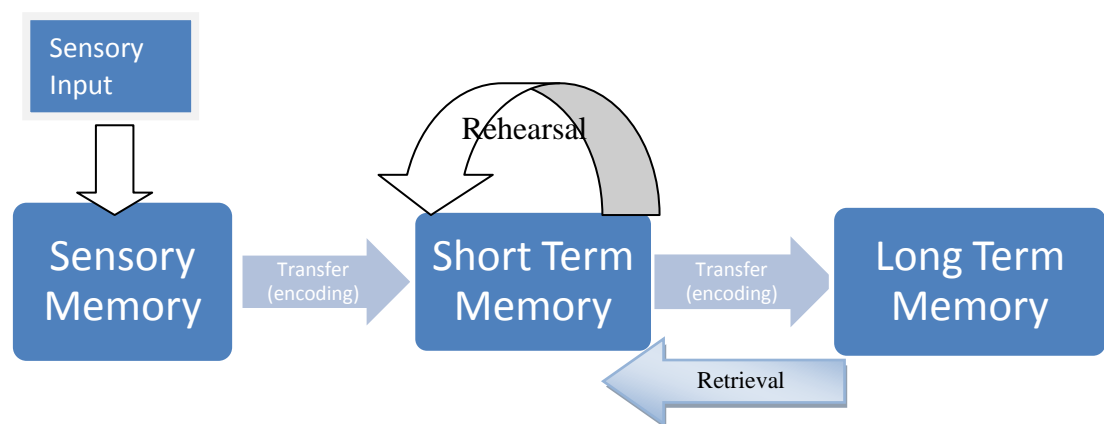


Figure 1.3: A general model of memory formation, storage, and retrieval based on the modal model of memory originally proposed by Atkinson and Shiffrin (1968). The likelihood that information will be transferred from short-term to long-term storage, or be encoded into long-term memory, was once thought to depend primarily on how long the person keeps the information active in short-term memory via rehearsal.

In this model, memory is transferred from a sensory memory to a short term memory store. The likelihood that information will be transferred from short term to long term memory storage, or be encoded into long term memory, was once thought to depend primarily on how long the person keeps the information active in short term memory via rehearsal. Although rehearsal clearly influences the transfer of information into long term memory storage, other factors, such as the depth of processing (i.e., the level of true understanding and manipulation of the information), attention, motivation, and arousal also play important roles (**Craik & Lockhart, 1972; Otten *et al.*, 2001; Eichenbaum, 2002**).

Baddeley & Hitch (1974) expanded upon this concept and proposed a tripartite working memory model that includes a central executive and two 'slave systems'; the phonological loop and the visuospatial sketchpad or store (**Figure 1.2**).

The phonological loop contains two elements; (1) short-term phonological storage of sounds and (2) an articulatory loop that maintains and rehearses information either vocally or subvocally. **Baddeley** and colleagues (**1974**) viewed its primary purpose as evolving for language acquisition and comprehension (**Baddeley et al., 1998**). In the laboratory, phonological storage has been traditionally measured by the Digit-Span Task, a subtest of the Wechsler Adult Intelligence Scale (WAIS) and the Ray Auditory Verbal Learning Task (RAVLT) amongst others (**Table 1.5**).

The visuospatial sketchpad or store was hypothesized to involve the maintenance and integration of visual ('what' information, like objects) and spatial ('where' information, like location in space) elements and a means of refreshing it by rehearsal (**Baddeley & Logie, 1999**). In laboratory conditions, this has been measured by the Rey Osterreith Complex Figure Test (RCFT), Spatial Span from the CANTAB tests and the Weschler Memory Scale Revised (WMRS) amongst others (**Table 1.5**).

There are many different models describing variations of the long-term memory domain. The two major subdivisions used are explicit and implicit long term memory. Although understanding these differences is helpful, the divisions are fluid (i.e. different forms of memory often mix and mingle) (**Coolidge & Wynn, 2005**). Whether short term working memory stores constitute a separate anatomical and functional system from long term memory or whether they are activated parts of long term-memory is debatable (**Miyake & Shah, 1999; Ruchkin et al., 2003**). Nevertheless, long-term memory storage and retrieval is an integral part of working memory (**O'Reilly et al., 1999**).

(1) *Explicit or declarative memory* requires conscious thought (e.g. such as recalling who came to dinner last night) and it is what most people have in mind when they think of 'memory'. This is further divided into episodic and semantic memory.

Episodic or autobiographical memory provides us with a crucial record of our personal or autobiographical experiences. Semantic memory accounts for our 'textbook learning' or general knowledge about the world. As with episodic memory, semantic memory ranges from strong (recall) to weak (familiarity) but unlike episodic memory, semantic memory is better sustained over time.

(2) *Implicit or procedural memory* (non-declarative memory) doesn't require conscious thought and allows you to do things automatically. This is also further divided into motor skill training and priming.

Motor skill acquisition enables us to carry out commonly learned tasks without consciously thinking about them. It's our 'how to' knowledge and examples include riding a bike and tying a shoe. Even what we think of as 'natural' tasks, such as walking, also require this type of procedural memory. Priming or conditioning occurs as a result of one's own personal experiences; if you have heard something very recently, or many more times than another thing, you are primed to recall it more quickly.

Table 1.5: Memory and learning

Main Domain	Subtypes	Other names	Definition	Examples of test
Directed Attention or Registration (1-2 seconds)	Sensory Peripheral Store (Sensory Memory)	(1) Visual or Iconic Memory	Retains large amount of information (see Table 1.4)	
		(2) Auditory or Echoic Memory		
Short Term Memory (1-20 minutes)	Immediate Memory	(1) Verbal Memory	Reproduction, recognition or recall of information directly or some time after presentation	LMT, RAVLT, CVLT, WAIS-III, VRM, WMSR, WRM, GNT, DFDBT, TBT
		(2) Visuospatial (non verbal) Memory	Allow information to be evaluated and perhaps stored longer through rehearsal and coding	SWM, SSP, DMS, PRM, PAL, BVRT, PAL, SRM, WMSR, RCFT, PASAT, WAIS-III
Long Term Memory	Explicit (Declarative) Memory	(1) Autobiographical, Episodic or Event Memory	Records details salient to individuals life Needs conscious thinking 'Knowing that'	PRM, SRM, CVLT, RAVLT, PAL, RCFT, WMSR WAIS-III (Vocabulary)
		(2) Semantic Memory	Meaning of words and concepts or propositional knowledge (facts)	RCFT, COWAT, GNT, WMSR, RBMT
	Implicit (Non Declarative) or Procedural Memory	(1) Motor skill training	Does not need conscious thinking 'Knowing how'	
		(2) Priming or classical conditioning		

BVRT=Benton Visual Retention Test, COWAT= Controlled Oral Word Association Test, CVLT= California Verbal Learning Test, DFDBT= Digit Forward and Digit Backwards Test, DMS=Delayed Matching to Sample (CANTAB), GNT=Graded Name Test (CANTAB), LMT= Logical memory Test, SRM=Spatial Recognition Memory (CANTAB), PAL= Paired Associate Learning (CANTAB), PASAT= Paced Auditory Serial Addition Task, PRM= Pattern Recognition Memory (CANTAB), RAVLT= Rey Auditory Verbal Learning Test, RBMT= Rivermead Behavioural Memory Test, RCFT= Rey Complex Figure Test, SWM=Spatial Working Memory (CANTAB), SSP=Spatial Span (CANTAB), TBT= Two Back Test, VRM= Verbal Recognition Memory (CANTAB), WAIS-III= Weschler Adult Intelligence Scale Third Edition, WMSR= Weschler Memory Scale Revised, WRM= Word Recognition Memory.

Quality and Validity assessment

For all review questions, data were extracted by one reviewer and checked by a second reviewer. Discrepancies were resolved by referral to the original studies. If necessary, arbitration was by a third reviewer. Duplicate publications were actively screened for and the latest or most complete report used for further analysis. The quality assessment checklist used was sourced from the Effective Public Health Practice Project, McMaster University (EPHPP) (**Appendix 2**).

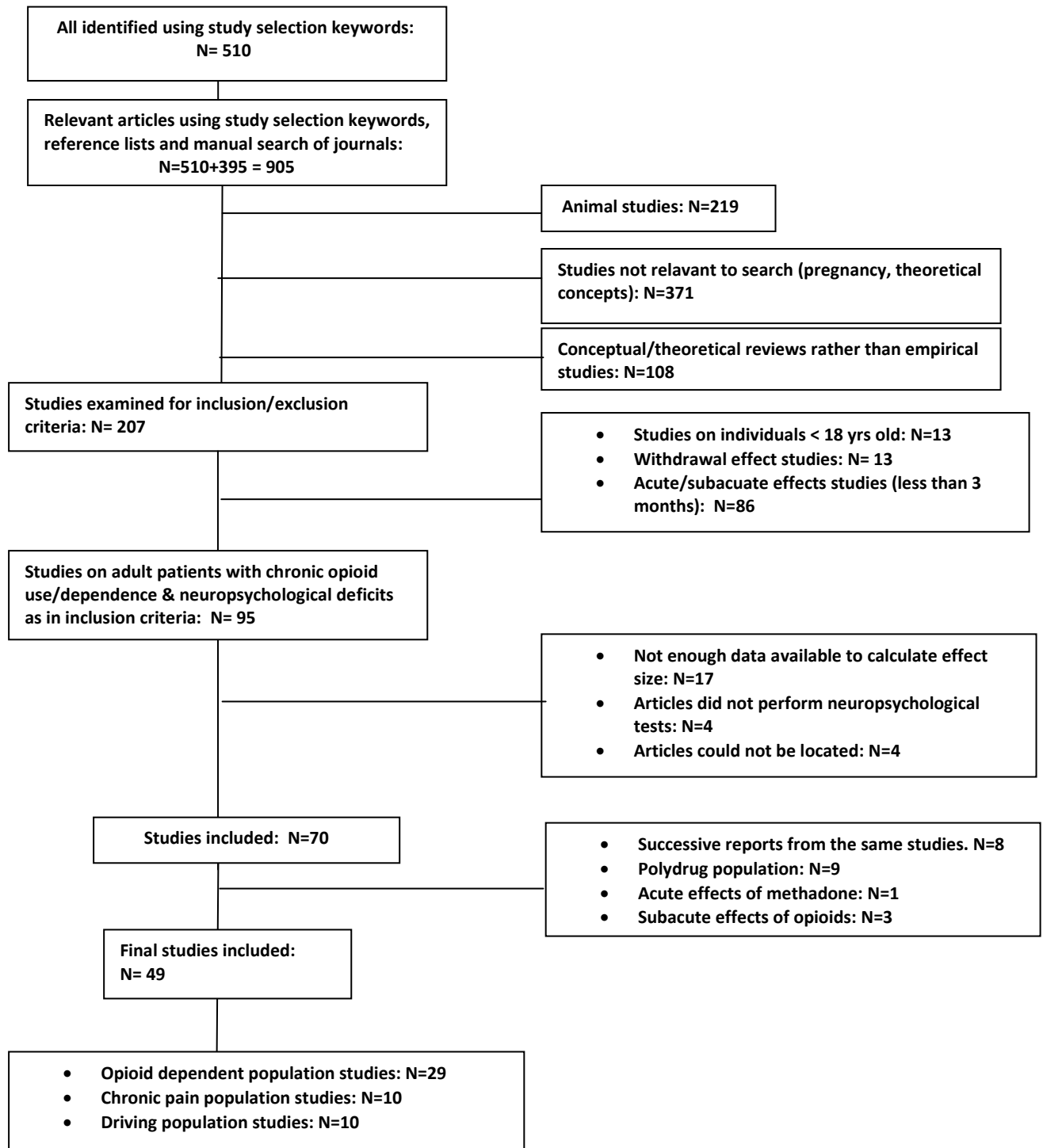
Results

Included and Excluded Studies

The literature search identified a number of articles relevant to chronic opioid use and neuropsychological consequences. The abstracts identified through the electronic and further searching were subjected to a 'selection and classification stage'. All abstracts extracted were merged together with the aim of excluding duplication of citations. Nine hundred and five (905) articles were then further analysed to identify relevant articles that satisfied the inclusion criteria. A total of ninety five (95) abstracts were then selected (**Figure 1.4**).

From the total number of abstracts (95), only seventy (70) studies could be used for the systematic review which also included four articles that could not be located. From these seventy studies eligible for this systematic review there were eight (8) articles that had reports published in different journals but using the same cohorts and instruments. A further nine (9) studied a polydrug population, one (1) study looked at the acute effects of methadone and three (3) other studies looked at subacute effects of opioid use on neuropsychological performance (**Appendix 3**).

Figure 1.4: Neuropsychological consequences of chronic opioid use: Quality of reporting of meta-analysis (QUOROM).



The remaining forty nine (49) studies were categorized into three distinct population groups (**Table 1.6**):

- (1) Opioid dependent population studies (N=29).
- (2) Chronic malignant and non malignant pain population studies (N=10).
- (3) Driving population studies (n=10).

Table 1.6: Number and type of cohort and controls used in the 49 selected studies.

Cohort	Substance Misuse Studies N= 29	Chronic Pain Studies N= 10	Driving Related Studies N= 10	TOTAL
Methadone Maintained Programme (MMP)	14	0	5	19
Heroin users	4	1	0	5
Abstinent previously opioid users	6	0	0	6
Methadone and Buprenorphine	2	0	1	3
Buprenorphine only	1	0	0	1
Morphine or Fentanyl users	0	8	3	11
Mixture of heroin, buprenorphine, fentanyl, oxycodone and/or methadone users	2	1	1	4
Controls*				
Healthy	21	4	6	31
Abstinent opioid users	9	1	0	10
Heroin users	1	0	0	1
Methadone Maintained Programme (MMP)	2	0	0	2
Buprenorphine users	0	0	2	2
Alcohol users	2	0	0	2
Amphetamine users	5	0	0	5
Chronic pain	1	3	0	4
Psychiatric	0	0	0	0
DLM-PFC/ Low Tryptophan/	2	0	0	2
Head Injury/Epilepsy	1	0	1	2
None	2	2	1	5

*= Some studies used more than one type of control, DLM-PFC= *Patients with focal lesions of Dorsolateral and Medial Prefrontal Cortex.*

Quality threshold

Out of the forty nine studies identified twenty eight (28) studies met moderate level in quality threshold and twenty one (21) studies were judged to be of weak quality. There were no strong quality studies. The twenty one studies judged to be of weak quality were excluded in the subsequent review analysis (**Tables 1.7a, b &c; Appendix 3**).

Table 1.7a: Quality threshold of the selected studies in the substance using population (N=29).

Study	Selection Bias	Study Design	Confounders	Blinding	Data Collection Methods	Withdrawal Dropouts	Global Rating
Mintzer <i>et al</i> (2005)	Moderate	Moderate	Strong	Moderate	Strong	Moderate	MODERATE
Lombardo <i>et al</i> (1976)	Moderate	Moderate	Moderate	Moderate	Strong	Weak	MODERATE
Gritz <i>et al</i> (1975)	Weak	Moderate	Strong	Weak	Strong	Weak	WEAK
Darke <i>et al</i> (2000)	Moderate	Moderate	Strong	Weak	Strong	Strong	MODERATE
Rotherhan-Fuller <i>et al</i> (2004)	Moderate	Moderate	Strong	Weak	Strong	Strong	MODERATE
Guerra <i>et al</i> (1987)	Strong	Moderate	Weak	Weak	Strong	Strong	WEAK
Rounsaville <i>et al</i> (1982)	Strong	Moderate	Strong	Moderate	Strong	Strong	MODERATE
Davis <i>et al</i> (2002)	Weak	Moderate	Strong	Weak	Strong	Strong	WEAK
Gruber <i>et al</i> (2006a)	Strong	Moderate	Strong	Weak	Weak	Weak	WEAK
Prosser <i>et al</i> (2006)	Strong	Moderate	Strong	Weak	Strong	Strong	MODERATE
Pirastu <i>et al</i> (2006)	Strong	Moderate	Strong	Weak	Strong	Strong	MODERATE
Hill & Mikhael (1979)	Moderate	Moderate	Strong	Strong	Strong	Strong	MODERATE
Strang & Gurling (1989)	Strong	Moderate	Weak	Weak	Strong	Strong	WEAK
Kelley <i>et al</i> (1978)	Weak	Strong	Strong	Strong	Strong	Weak	WEAK
Soyka <i>et al</i> (2008)	Strong	Moderate	Strong	Weak	Strong	Moderate	MODERATE
Brand <i>et al</i> (2008)	Strong	Moderate	Strong	Weak	Strong	Strong	MODERATE
Passetti <i>et al</i> (2008)	Strong	Moderate	Moderate	Moderate	Moderate	Strong	MODERATE
Petry <i>et al</i> (1998)	Strong	Moderate	Strong	Weak	Strong	Weak	WEAK
Stevens <i>et al</i> (2007)	Moderate	Moderate	Strong	Moderate	Strong	Strong	MODERATE
Gordon (1970)	Weak	Moderate	Weak	Weak	Weak	Weak	WEAK
Fishbein <i>et al</i> (2005a)	Strong	Moderate	Strong	Weak	Strong	Strong	MODERATE
Fishbein <i>et al</i> (2007)	Strong	Moderate	Strong	Weak	Strong	Strong	MODERATE
Verdejo <i>et al</i> (2007a)	Moderate	Moderate	Strong	Moderate	Strong	Weak	MODERATE
Verdejo <i>et al</i> (2007b)	Moderate	Moderate	Strong	Moderate	Strong	Weak	MODERATE
Ornstein <i>et al</i> (2000)	Strong	Moderate	Strong	Moderate	Strong	Strong	MODERATE
Rogers <i>et al</i> (1999a)	Strong	Moderate	Strong	Moderate	Strong	Strong	MODERATE
Clark <i>et al</i> (2006)	Strong	Moderate	Strong	Moderate	Strong	Strong	MODERATE
Ersche <i>et al</i> (2005a)	Strong	Moderate	Strong	Moderate	Strong	Strong	MODERATE
Ersche <i>et al</i> (2006a)	Strong	Moderate	Strong	Moderate	Strong	Strong	MODERATE

Table 1.7b: Quality threshold of the selected studies in the chronic pain population (N=10).

Study	Selection Bias	Study Design	Confounders	Blinding	Data Collection Methods	Withdrawal Dropouts	Global Rating
Sjogren <i>et al</i> (2005)	Moderate	Moderate	Moderate	Moderate	Strong	Strong	MODERATE
Sjogren <i>et al</i> (2000a)	Strong	Moderate	Moderate	Weak	Strong	Weak	WEAK
Sjogren <i>et al</i> (2000b)	Strong	Moderate	Moderate	Weak	Strong	Moderate	WEAK
Banning & Sjogren (1990)	Weak	Moderate	Weak	Weak	Strong	Weak	WEAK
Clemons <i>et al</i> (1996)	Weak	Moderate	Moderate	Weak	Strong	Weak	WEAK
Wood <i>et al</i> (1998)	Weak	Moderate	Moderate	Weak	Moderate	Moderate	WEAK
McNairy <i>et al</i> (1984)	Moderate	Moderate	Moderate	Moderate	Strong	Strong	MODERATE
Jamison <i>et al</i> (2003)	Moderate	Moderate	Strong	Weak	Strong	Strong	MODERATE
Haythornthwaite <i>et al</i> (1998)	Weak	Moderate	Moderate	Weak	Moderate	Weak	WEAK
Tassain <i>et al</i> (2003)	Moderate	Moderate	Moderate	Weak	Strong	Strong	MODERATE

Table 1.7c: Quality threshold of the selected studies in the driving population (N=10).

Study	Selection Bias	Study Design	Confounders	Blinding	Data Collection Methods	Withdrawal Dropouts	Global Rating
Soyka <i>et al</i> (2005)	Weak	Strong	Strong	Weak	Strong	Moderate	WEAK
Soyka <i>et al</i> (2001)	Weak	Moderate	Weak	Weak	Strong	Weak	WEAK
Vainio <i>et al</i> (1995)	Strong	Moderate	Moderate	Weak	Strong	Moderate	MODERATE
Byas-Smith <i>et al</i> (2005)	Weak	Moderate	Weak	Moderate	Weak	Moderate	WEAK
Galski <i>et al</i> (2000)	Strong	Moderate	Moderate	Weak	Weak	Weak	WEAK
Schindler <i>et al</i> (2004)	Weak	Moderate	Strong	Moderate	Strong	Weak	MODERATE
Specka <i>et al</i> (2000)	Strong	Moderate	Strong	Weak	Strong	Strong	MODERATE
Staak <i>et al</i> (1993)	Weak	Moderate	Weak	Weak	Strong	Weak	WEAK
Hornung <i>et al</i> (1996)	Strong	Moderate	Weak	Weak	Strong	Weak	WEAK
Bukasa <i>et al</i> (2006)	Weak	Moderate	Weak	Weak	Strong	Weak	WEAK

Background information of selected studies (N=28)

Tables 1.8 and 1.9 describe the participants, measures and procedures employed by each of the twenty eight identified and selected studies. There were a mean number of 39.2 cohorts and 563.9 healthy controls per study. The studies were all conducted in an urbanized setting. Eighteen (68%) studies were conducted in Europe, predominantly in the UK, nine (29%) studies in the USA and one (3.2%) in Australia. All the studies were published in English speaking journals (**Tables 1.8 a&b; Tables 1.9 a&b**). There was a wide variation in the period of data collection and most were case controlled studies attending a drug dependence clinical setting. Most of the cohorts were considered as dependent on opioids with the exception of four studies where the cohort had a diagnosis of non malignant chronic pain prescribed opioids but not dependent. The studies were biased towards the male gender with an average ratio of 2 males to 1 females (n=28). The mean age of the cohorts was 33.9 years (n=27) with a mean educational attainment of 11.1 years (n=19).

Mean duration of chronic opioid use was 8.5 years (n=22) with a mean morphine equivalent daily dosage available only in seventeen studies. For the thirteen (13) studies with a history of drug dependence the mean dose was 588.62mg daily and for the four studies looking at the chronic pain population the morphine equivalent dose was 95.58mg daily. Chronic opioid use spanned between 15 and 0.26 years .

Neuropsychological tests and outcomes from these selected studies were grouped into the composite neuropsychological domains as discussed earlier in this chapter (**Table 1.10**).

Table 1.8a: Generic guidelines in substance using population (N=21).

Study	Country of study	Period of data collection (months)	Study design hierarchy	Cohort (N)	Control (N) and type
Mintzer <i>et al</i> (2005)	USA	36	3b	18	20 Healthy
Lombardo <i>et al</i> (1976)	USA	n/a	4	20 Methadone 80mg	18 Methadone 50mg
Darke <i>et al</i> (2000)	Australia	n/a	3b	30	30 Healthy
Rotherham Fuller <i>et al</i> (2004)	USA	n/a	3b	18	19 Healthy
Rounsaville <i>et al</i> (1982)	USA	n/a	3b	72	29 Healthy
Prosser <i>et al</i> (2006)	USA	n/a	3b	29	56 Abstinent
Pirastu <i>et al</i> (2006)	Italy	n/a	3b	30 Meth, 18 Bup	21 Healthy
Hill & Mikhael (1979)	USA	n/a	3b	15	15 Alcohol 15 Healthy
Soyka <i>et al</i> (2008)	Germany	n/a	1	24 Meth, 22 Bup	24 Healthy
Brand <i>et al</i> (2008)	Germany	n/a	3b	18	18 Healthy
Passetti <i>et al</i> (2008)	UK	n/a	3b	10	27 Healthy
Stevens <i>et al</i> (2007)	Germany	n/a	3b	25	26 Abstinent 26 Healthy
Fishbein <i>et al</i> (2005a)	USA	n/a	3b	13	14 healthy
Fishbein <i>et al</i> (2007)	Russia	24	3b	100	102 Alcohol 60 Alcohol & Opiate 160 Healthy
Verdejo Garcia <i>et al</i> (2007a)	Spain	n/a	3b	81	37 Healthy
Verdejo Garcia <i>et al</i> (2007b)	Spain	n/a	3b	64	30 Healthy
Ornstein <i>et al</i> (2000)	UK	12	3b	22	23 Amp 25 Healthy
Rodgers <i>et al</i> (1999a)	UK	12	3b	13	18 Amp 10 ORB-PFCPFC 10 DLM –PFC 26 Healthy
Clark <i>et al</i> (2006)	UK	n/a	3b	40	24 Amp 24 Abstinent 26 Healthy
Ersche <i>et al</i> (2005a)	UK	n/a	3b	27 Heroin, 12 Bup	24 Amp 26 Abstinent 27 Healthy
Ersche <i>et al</i> (2006a)	UK	n/a	3b	42	25 Amp 27 Healthy 26 Abstinent

1= Experimental studies, 2=Quasi-experimental studies (e.g. experimental study without randomisation), 3a=Cohort studies, 3b=Case control studies, 4=Observational studies without control groups, Amp=Amphetamines, Bup= Buprenorphine, DLM-PFC=Dorsolateral/Medial Prefrontal Cortex , Meth=Methadone, ORB-PFC= Orbital Prefrontal Cortex, , n/a =information not available, N= Number, USA= United States of America, UK= United Kingdom.

Table 1.8b: Generic guidelines in chronic pain and driving populations (N=7).

Study	Country of study	Period of data extraction (months)	Study design hierarchy	Cohort (N)	Control (N) and type
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Chronic Pain Population Studies (N=4)

Sjogren <i>et al</i> (2005)	Denmark	12	3a	91	64 Healthy
McNairy <i>et al</i> (1984)	USA	n/a	3b	33	14 Healthy
Jamieson <i>et al</i> (2003)	USA	n/a	1	114	Cross over trial
Tassain <i>et al</i> (2003)	France	n/a	3b	18	10 Healthy

Driving Population Studies (N=3)

Vainio <i>et al</i> (1995)	Finland	n/a	3b	24	25 Healthy
Schindler <i>et al</i> (2004)	Austria	n/a	3b	15	14500 Healthy
Specka <i>et al</i> (2000)	Germany	n/a	3b	54	54 Healthy

1= Experimental studies, 2=Quasi-experimental studies (e.g. experimental study without randomisation), 3a=Cohort studies, 3b=Case control studies, 4=Observational studies without control groups, Amp=Amphetamines, Bup= Buprenorphine, DLM-PFC=Dorsolateral/Medial Prefrontal Cortex, Meth=Methadone, ORB-PFC= Orbital Prefrontal Cortex, n/a =information not available, N= Number, USA= United States of America, UK= United Kingdom.

Table 1.9a: Specific guidelines in substance using population (N= 21).

Study	Age (yrs)	M:F	Ethnic	R:L	Education (yrs)	Opioid Use (yrs)	Dosage (morph equivalent)	Types of opioids	Service	Diagnosis	Measures (Psych/Depend/Pain)
Mintzer <i>et al</i> (2005)	37.6	2:1	28%	n/a	11.8	15.3	670mg	Meth	CDT	OD	n/a
Lombardo <i>et al</i> (1976)	32.1	1:0	n/a	n/a	11.4	n/a	800mg	Meth	CDT	OD	DSM IV(D)
Darke <i>et al</i> (2000)	35.8	3:2	n/a	n/a	11.2	n/a	786mg	Meth	CDT	OD	CIDI(D), DSM IV(D)
Rotherham- Fuller <i>et al</i> (2004)	41.7	n/a	22%	n/a	11.8	n/a	680mg	Meth Smokers	Inpatient	OD	DSM IV (D),BDI (S),SCID R II(D), ADHD (S),ASI (D)
Rounsaville <i>et al</i> (1982)	27.9	2:1	58%	9:1	11.5	8.2	n/a	Meth	Inpatient	OD	MMPI (S),ICD9(D), SCL-90 (S), BDI (S)
Prosser <i>et al</i> (2006)	38.0	4:1	38%	n/a	13	21	730mg	Her and Meth	Inpatient & Rehab	OD	DSM III (D), SUI (S)
Pirastu <i>et al</i> (2006)	34.0	2 F	n/a	n/a	8.27	n/a	n/a	Meth and Bup	CDT	OD	DSM III (D)
Hill & Mikhael (1979)	29.2	n/a	0%	n/a	11.5	8.6	n/a	Her	CDT	OD	FC (D)
Soyka <i>et al</i> (2008)	n/a	n/a	n/a	n/a	n/a	n/a	n/a	Meth and Bup	CDT	OD	
Brand <i>et al</i> (2008)	31.1	7:2	n/a	n/a	9.3	11.6	n/a	Abst Her	Rehab	OD	DSM IV SCI (D), FPI (S)
Passetti <i>et al</i> (2008)	37.7	7:3	n/a	n/a	n/a	10.2	400mg	Meth	CDT	OD	DSM IV SCI(D),YMRS(S),BDI(S),BPRS (S),MAP(S)
Stevens <i>et al</i> (2007)	30.4	1:0	n/a	1:0	11.3	9.5	476mg	Her	CDT and Rehab	OD	BDI (S), TAF (S), STAI (S), SHAPS (S)
Fishbein <i>et al</i> (2005a)	27.3	7:6	39%	1:0	n/a	9.4	n/a	Abst Her	Rehab	OD	DI (D), PCL-R (S), SCL-9R (S), ASI, (D)
Fishbein <i>et al</i> (2007)	25.6	2:1	100%	n.a	11	6.3	n/a	Abst Her	Rehab	OD	DSM IV-SCI (D), ASI (D), BPRS (S),16PF
Verdejo-Garcia <i>et al</i> (2007a)	30.9	76:5	100%	n/a	9.8	9.2	n/a	Abst Her	Rehab	OD	
Verdejo-Garcia <i>et al</i> (2007b)	29.8	n/a	100%	n/a	9.42	n/a	n/a	Abst Her	Rehab	OD	
Ornstein <i>et al</i> (2000)	33.3	1:0	100%	n/a	11.9	11.6	n/a	Her and Meth	CDT	OD	
Rodgers <i>et al</i> (1999a)	34.5	1:0	100%	n/a	n/a	13.9	395mg	Her and Meth	CDT	OD	
Clark <i>et al</i> (2006)	34.0	4:1	100%	n/a	n/a	11	428mg	Meth	CDT	OD	BDI (S)
Ersche <i>et al</i> (2005a)	33	4:1	100%	9:1	n/a	9.2	450mg	Meth and Her	CDT	OD	BDI (S)
Ersche <i>et al</i> (2006a)	33.8	4:1	100%	9:1	n/a	10.8	450mg	Her,Meth,Bup	CDT	OD	BDI (S)

Abst Her= Abstinient Heroin, bup=buprenorphine , CDT= Community Drug Team , D= Diagnostic , Ethnic= Ethnicity , , F/up= Follow up period when neuropsychological outcomes measured after baseline, her= heroin ,M:F= Male: Female, m/meth= methadone, morph= morphine , n/a= not available, OD= opioid dependence , other= dihydrocodeine, tramadol and/or oxycodone, R:L= Right:Left Handdendeness, S= Screening, rehab= rehabilitation, yrs= years.

ADHD= Attention Deficit Hyperactivity Disorder Scale , BDI=Beck Depression Inventory , BPRS= Brief Psychiatric Rating Scale, Cattell 16PF= Cattell 16 Personality Factor Assessment , CIDI =Composite International Diagnostic Index , DI=Dysregulation Inventory ,DSM IV/III = Diagnostic and Statistical Manual of Mental Disorders 4th/3rd Edition, Euro ASI= European version of Addiction Severity Index , Fager= Fagerstrom Test of Nicotine Dependence , FC= Feighner Criteria , FPI= Freiburg Personality Inventory , HDRS=Hamilton Depression Rating Scale , ICD-9= International Classification of Disorders 9th Edition, MAACL= Multiple Affect Adjective Check List , MAP= Maudsley Addiction Profile , McGill=Melzack's McGill Pain Questionnaire ,MMPI= Minnesota Multiphasic Personality Inventory ,MMSE=Mini Mental State Examination , PCL-R=Psychopathy Checklist-Revised ,PVAS=Pain Visual Analogue Scale ,SCID R III =Structured Clinical Inventory –Revised for DSM-III, SCL-90R= Symptom Checklist-90-Revised, SHAPS = Snaith-Hamilton Pleasure Scale , STAI =State-Trait-Anxiety Inventory ,SUI= Substance Use Inventory,TAF= Tübingen Anhedonia Questionnaire, Wang Scale= Opiate withdrawal scale, WURS = Wender Utah Rating Scale ,W-VAS= Visual Analogue Mood Scale, YMRS=Young Mania Rating Scale.

Table 1.9b: Specific guidelines in chronic pain and driving populations (N= 7).

Study	Age (yrs)	M:F	Ethnic	R:L	Education (yrs)	Opioid Use (yrs)	Dosage (morph equivalent)	Types of opioids	Service	Diagnosis	Measures (Psych/Depend/Pain)
Sjogren <i>et al</i> (2005)	44.4	1:1	100%	n/a	13.2	7	n/a	Morph	Pain	Non malignant chronic pain	MMSE (S), PVAS (S)
McNairy <i>et al</i> (1984)	46.0	5:4	n/a	n/a	n/a	9	25.5mg	Her	Pain	OD with chronic pain	MMPI (S), PVAS (S) ICD-9 (D)
Jamieson <i>et al</i> (2003)	46.3	2:1	90%	n/a	11	0.49	75.85mg	Oxycodone & Fentanyl	Pain	Non malignant chronic pain	BDI (S) , PVAS (S)
Tassain <i>et al</i> (2003)	46.0	5:4	n/a	n/a	12.0	1	72mg	Morph	Pain	Non malignant chronic pain	BDI (S), HDRS (S) PVAS STAI (S), W-VAS (S) McGill. (S)
Vainio <i>et al</i> (1990)	53	1:1	n/a	n/a	11	0.26	209mg	Morph	Oncology	Chronic malignant pain	MAACL (S) ICD-9 (D)
Schindler <i>et al</i> (2004)	25.8	3:2	n/a	n/a	n/a	5.8	457mg	Meth & Bup	CDT	OD	Euro ASI (D), Wang Scale (S)
Specka <i>et al</i> (2000)	29.0	2:1	n/a	n/a	11	8	930mg	Meth	CDT & Psychiatric	OD	FPI (S)
Vainio <i>et al</i> (1990)	53	1:1	n/a	n/a	11	0.26	209mg	Morph	Oncology	Chronic malignant pain	MAACL (S) ICD-9 (D)

Abst Her= Abстинent Heroin, bup=buprenorphine , CDT= Community Drug Team , D= Diagnostic , Ethnic= Ethnicity, , F/up= Follow up period when neuropsychological outcomes measured after baseline, her= heroin, M:F= Male: Female, m/meth= methadone, morph= morphine , n/a= not available, OD= opioid dependence , other= dihydrocodeine, tramadol and/or oxycodone, R:L= Right:Left Handedness, S= Screening, rehab= rehabilitation, yrs= years. ADHD= Attention Deficit Hyperactivity Disorder Scale , BDI=Beck Depression Inventory , BPRS= Brief Psychiatric Rating Scale, Cattell 16PF= Cattell 16 Personality Factor Assessment , CIDI =Composite International Diagnostic Index , DI=Dysregulation Inventory , DSM IV/III = Diagnostic and Statistical Manual of Mental Disorders 4th/3rd Edition, Euro ASI= European version of Addiction Severity Index , Fager= Fagerstrom Test of Nicotine Dependence , FC= Feighner Criteria , FPI= Freiburg Personality Inventory , HDRS=Hamilton Depression Rating Scale , ICD-9= International Classification of Disorders 9th Edition, MAACL= Multiple Affect Adjective Check List , MAP= Maudsley Addiction Profile , McGill=Melzack's McGill Pain Questionnaire ,MMPI= Minnesota Multiphasic Personality Inventory ,MMSE=Mini Mental State Examination , PCL-R=Psychopathy Checklist-Revised ,PVAS=Pain Visual Analogue Scale ,SCID R III =Structured Clinical Inventory –Revised for DSM-III, SCL-90R= Symptom Checklist-90-Revised, SHAPS = Snaith-Hamilton Pleasure Scale , STAI =State-Trait-Anxiety Inventory ,SUI= Substance Use Inventory,TAF= Tübingen Anhedonia Questionnaire, Wang Scale= Opiate withdrawal scale, WURS = Wender Utah Rating Scale ,W-VAS= Visual Analogue Mood Scale, YMRS=Young Mania Rating Scale.

Table 1.10: Neuropsychological outcomes.

Study	Short Term Memory	Long Term Memory	Cognitive Flexibility	Attention	Intelligence	Motor Impulsivity	Non-Planning Impulsivity	Cognitive Impulsivity
Substance Misuse Population								
Mintzer <i>et al</i> (2005)	2BT ↓	n/a	TMT↓	DSST↓	SILS↔	n/a	n/a	IGT ↓
Lombardo <i>et al</i> (1976)	n/a	n/a	n/a	WAIS II↔	WAIS II↔	n/a	n/a	n/a
Darke <i>et al</i> (2000)	WMSR,CVLT,RCFT↓	n/a	COWAT, WCST↓	WAIS II↓	WAIS II↓	n/a	n/a	n/a
Rotherham-Fuller <i>et al</i> (2004)	n/a	n/a	WCST↔	n/a	SILS↔	n/a	n/a	IGT↓
Rounsaville <i>et al</i> (1982)	n/a	n/a	TMT↔	DSST↔	WAIS II ↔	GP↔	n/a	n/a
Prosser <i>et al</i> (2006)	BVRT↓	n/a	COWAT↔,ST↓	n/a	WAIS III↓	n/a	n/a	n/a
Pirastu <i>et al</i> (2006)	BVRT↓	n/a	WCST↓	n/a	WAIS III↓	n/a	n/a	IGT↓
Hill & Mikhael (1979)	n/a	n/a	CT↔,TMT↓	n/a	SILS↔	n/a	n/a	n/a
Soyka <i>et al</i> (2008)	AVLT↓	n/a	RWT,TMT↓	DR2↓	n/a	n/a	n/a	n/a
Brand <i>et al</i> (2008)	n/a	n/a	FAS ↔,MCST↓	n/a	LPS↓	FWIT↓	TOH ↔	GDT↓
Passetti <i>et al</i> (2008)	n/a	n/a	n/a	n/a	WTAR↔	Go-NoGo	TOL↔	CGT,IGT,IST↓, DDT↔
Stevens <i>et al</i> (2007)	WMSR,DMS↔	WMSR↔	TMT↓	SRTT↓	MWT-B↔	n/a	n/a	n/a
Gordon <i>et al</i> (1970)	n/a	n/a	n/a	SRT↑	WAIS III↔	n/a	n/a	n/a
Fishbein <i>et al</i> (2005a)	n/a	n/a	n/a	n/a	SILS↓	n/a	n/a	RDMT↓
Fishbein <i>et al</i> (2007)	PAL, DMS↓	PAL↓	SCT, ST↓	n/a	RPM ↓	n/a	SOC↓	RDMT↓
Verdejo Garcia <i>et al</i> (2007a)	WMSR,WAIS III,CBT↓	n/a	FAS,RFFT,WCST, ST, CT↓	WAISIII,5DT↓	WAIS III↔	Go-NoGo↓	n/a	IGT ↓

Verdejo Garcia <i>et al</i> (2007b)	n/a	n/a	ST↓	5DT↔	WAT↔	Go-NoGo↓	n/a	IGT↓
Ornstein <i>et al</i> (2000)	SRM ↔,SWM↓	PRM ↔	VFT, IED↓	n/a	NART↔	n/a	TOL↓	n/a
Rodgers <i>et al</i> (1999a)	n/a	n/a	n/a	n/a	NART↔	n/a	n/a	CGT ↓
Clark <i>et al</i> (2006)	n/a	n/a	n/a	n/a	NART↔	n/a	n/a	IST,BIS↓
Ersche <i>et al</i> (2005a)	n/a	n/a	n/a	n/a	NART↔	n/a	n/a	CGT,BIS↓
Ersche <i>et al</i> (2006a)	PAL, PRM↓	PAL,PRM↓	IED↓	n/a	NART↔	n/a	SOC↓	n/a
Chronic Pain Population								
Sjogren <i>et al</i> (2005)	n/a	n/a	n/a	CRT,PASAT↓	n/a	FTT↓	n/a	n/a
McNairy <i>et al</i> (1984)	AVLT↔	n/a	TMT↔	WAIS II↔	WAIS II↔	FTT↓	n/a	n/a
Jamieson <i>et al</i> (2003)	n/a	n/a	TMT↑	WAISIII,DSST↔	n/a	n/a	n/a	n/a
Tassain <i>et al</i> (2003)	CVLT,WAIS III↔	CVLT↔	VFT, ST, TMT↔	WAIS III,SRT↔	n/a	n/a	n/a	n/a
Driving population								
Vainio <i>et al</i> (1995)	n/a	n/a	n/a	Q1↔	M30↔	RST3↔	LL5↔	n/a
Schindler <i>et al</i> (2004)	n/a	n/a	FAT↔	DR2,Q1↓	MAT↔	RST3↔	LL5↔	n/a
Specka <i>et al</i> (2000)	n/a	n/a	n/a	DR2,Q↔	n/a	RST3↓	LL5↔	n/a

n/a= not applicable, ↓= sig. deficits present, ↔= no sig.deficits present, ↑= sig.improvement observed at $p<0.05$.

AVLT= Auditory Verbal Learning Test ,BIS= Barrats Impulsivity Scale , BVRT= Benton Visual Retention Test, CBT=Cognitive Bias Test, COWAT/FAS= Controlled Oral Word Association Test/Phonological Fluency Test,CRT=Continuous Reaction Time, CVLT=California Verbal Learning Test, DDT= Delay Discounting Task, DSST=Digital Symbol Substitution Test ,FWIT= Farbe-Wort-Interferenz-Test (Word-Color-Interference Test), 5DT= Five Digit Test, GDT=Game and Dice Test, Go-NoGo=Go-NoGo Test, GP= Grooved Pegboard ,IGT= Iowa Gambling Task, IST=Information Sampling Task, LPS= Leistungs Prufsystem(German intelligence test battery), MWT-B= MehrfachwahlWortschatz-Intelligenz-Test (Multiple Choice Word Comprehension Test) MCST=Maudsley Card Sorting Test,NART= National Adult Reading Test ,PASAT= Paced Auditory Serial Addition Task, RPM= Raven's Progressive Matrices, RCFT=Rey Osterreith Complex Figure Test, RWT= Regensburger Word Fluency Test, SILS=Shipley Institute to Living Scale, ST=Stroop Test , TOH= Tower of Hanoi, 2BT= Two Back Task,RAVLT=Rey Auditory Verbal Learning Test, RFFT= Ruff Figural Fluency Test, SCT= (Logan) Stop Change Task ,SRTT=Serial Reaction Time Task, SRT= Simple Reaction Time, VFT= Verbal Fluency Test, WAIS III/II= Weschler Adult Intelligence Scale 3rd/2nd Edition, WCST= Wisconsin Card Sorting Test ,WMSR= Weschler Memory Scale Revised,WTAR= Weschler Test of Adult Reading, WAT= Word Accentuation Test.

CANTAB: DMS= Delayed Matching to Sample, PAL= Paired Associate Learning Task, PRM= Pattern Recognition Memory, SRM= Spatial Recognition Memory, SWM= Spatial Working Memory, SOC = Stockings of Cambridge, IED= Intra/Extra-Dimensional Set Shifting Task, CGT/RDMT= Cambridge Gambling Task/Roger's Decision Making Test, SST= Stop Signal Task, AGN= Affective Go-NoGo Test.Halstead Reitan Neuropsychological Test Battery: FTT= Finger Tapping Test, TMT= Trail Making Test, CT= Category Test. Act React Test Systems (ART 90/2020): FAT= Test of Attentional Flexibility, DR2=Simple Choice Reaction, Q1= Attention under Monotonous Circumstances, MAT/M30=Matrices for Intelligence Test, RST3=Multiple Choice under Stress, LL5=Labyrinth of Lines to Measure Visual Structuring Performance

Descriptive summary of findings

A large number of studies have been conducted which examine the effects of opioid use on a variety of neuropsychological skills and abilities. The population studied were either from the opioid dependent or chronic pain clinical settings. Most studies have attempted to target one opioid such as prescribed methadone or illicit heroin use. In addition to the literature on the chronic effects of heroin and methadone, some studies have examined neuropsychological functioning in the more general group of 'opioid addicts' by combining participants with current methadone, heroin and/or other opioid use. The progress in each of these areas will be examined in turn.

Intelligence in opioid dependent and using population

The first published study to examine the effects on intelligence in chronic methadone users was conducted by **Isbell *et al.*, (1948)**. This study examined 'general intelligence' in methadone users and concluded that 'methadone may have a detrimental impact on intellectual functioning'. **Gordon (1970)** reported that they had found no irregularities in the performance of methadone maintenance patients on the Wechsler Adult Intelligence Scale (WAIS).

Gordon & Lispet (1976) followed up an initial cohort approximately 112 months after their initial assessment. They repeated the WAIS assessment with thirty of these participants who were still receiving prescribed methadone and found that all participants' intellectual functioning remained in the average range.

Darke *et al.*, (2000) and **Prosser *et al.*, (2006)** both found low IQ and reduced verbal function in methadone users. While limited inference can be drawn from these cross-sectional studies of such a small number of participants, the results may suggest problems in achieving recovery within methadone maintenance for this group.

Several studies have suggested the existence of neuropsychological alterations prior to drug use that could act as causal or vulnerability factors (**Verheul, 2001**). This systematic review has described studies who have either adjusted for possible

differences between opioid users and controls, on intelligence and educational level (Ersche *et al.*, 2005a & 2006a; Darke *et al.*, 2000; Rotherham–Fuller *et al.*, 2004) or not (Prosser *et al.*, 2006).

Overall studies show conflicting evidence on the effects of intellectual function in participants with a history of opioid use and dependence either still on illicit heroin, treated with methadone, following a period of abstinence or using opioids for analgesic purposes. **Table 1.11** summarises the evidence presented in this review for an association between chronic opioid use and intellectual impairment.

Table 1.11: Summary of previous research regarding chronic opioid use and intelligence.

Studies	Intelligence tests and results*	Cohen's <i>d</i>
Brand <i>et al</i> (2008)	LPS:↓	0.99
Clark <i>et al</i> (2006)	Verbal IQ (WAIS):↔	0.28
Darke <i>et al</i> (2000)	Verbal IQ (WAIS): ↓	0.13
Ersche <i>et al</i> (2005a)	Verbal IQ (WAIS):↔	0.19 (Meth) & 0.23 (Heroin)
Ersche <i>et al</i> (2006a)	Verbal IQ (WAIS):↔	0.23 (Opioid) & 0.13 (Abstinent)
Fishbein <i>et al</i> (2005a)	SILS:↓	0.54
Fishbein <i>et al</i> (2007)	RPM:↓	0.75
Gordon (1970)	Verbal IQ (WAIS): ↔	0.43
Hill & Mikhael (1979)	SILS:↔	0.73
Lombardo <i>et al</i> (1976)	Verbal IQ (WAIS): ↔	0.43
Mintzer <i>et al</i> (2005)	SILS: ↔	2.40 (Meth)& 1.70 (Abstinent)
McNairy <i>et al</i> (1984)	Verbal IQ (WAIS):↔	0.00
Ornstein <i>et al</i> (2000)	NART:↔	0.44
Passetti <i>et al</i> (2008)	Verbal IQ (WTAR): ↔	0.95 (Meth vs Meth + Heroin)
Pirastu <i>et al</i> (2006)	Verbal IQ (WAIS):↓	6.97(Meth) & 4.30(Bup)
Prosser <i>et al</i> (2006)	Verbal IQ (WAIS): ↓	1.43 (Meth) & 1.09 (Abstinent)
Rogers <i>et al</i> (1999a)	NART:↔	3.09
Rotherham-Fuller <i>et al</i> (2004)	SILS: ↔	0.72 (Meth smoker) & 0.56 (Meth non smoker)
Rounsaville <i>et al</i> (1982)	Verbal IQ (WAIS): ↔	0.93
Schindler <i>et al</i> (2004)	MAT: ↔	n/c
Stevens <i>et al</i> (2007)	Verbal IQ (MWT-B): ↔	0.09 (Abstinent)
Vainio <i>et al</i> (1995)	M30: ↔	0.33
Verdejo-Garcia <i>et al</i> (2007a)	WAT:↔	0.42
(2007b)	WAT:↔	0.40

Meth= Methadone, Bup=Buprenorphine, n/c= controls not healthy controls or not enough information to calculate effect size ↓= Deficits present, ↔= no deficits present, ↑= improvement observed at **p*<0.05 when compared with healthy controls.

LPS= *Leistungs Prufsystem*(German intelligence test battery), MAT/M30=Matrices for Intelligence Test (Part of Act React Test Systems: ART 90/2020), MWT-B= *MehrfachwahlWortschatz-Intelligenz-Test* (Multiple Choice Verbal ComprehensionTest), NART= *National Adult Reading Test*, RPM= *Raven's Progressive Matrices*, SILS=Shipley Institute to Living Scale, WAIS = *Weschler Adult Intelligence Scale*, WTAR= *Weschler Test of Adult Reading*, WAT= *Word Accentuation Test* (similar to NART in Spanish).

Neuropsychological functioning in opioid dependent and using population

The results of such studies are difficult to interpret as these groups often contain individuals who abuse various different opioids, and it is therefore not possible to attribute observed deficits to the effects of any specific type of opioid. However as many individuals in this population will use a variety of different opioids in their

lifetime, these studies may help to examine whether there is a neuropsychological profile characteristic of this population.

An early example of this type of research was conducted by **Rounsaville *et al.*, (1982)** who assessed a group of 72 opioid addicts upon entering treatment, using a brief neuropsychological battery. This group consisted of individuals who were still using illicit heroin, those who had recently commenced on a prescribed methadone dose, and those who had recently been detoxified from all opioids. Many of these individuals could be classified as poly-drug users, reporting regular use of other substances including amphetamines, cocaine, sedatives, cannabis and alcohol. The group varied widely in terms of the length and nature of their drug abuse.

The authors found that although the opioid group's intellectual functioning scores was in the normal range, their performance in a number of areas of neuropsychological functioning was at the mildly impaired range. These included tasks of attention, cognitive flexibility and motor impulsivity. When the opioid group were compared to a control group of non substance using participants matched for sociodemographic variables, the former did not perform significantly below the latter group on any of the measures included. Six months after the initial assessment, the authors noted that the improvements observed could not be attributed to the effects of detoxification from opioids as more than half of the sample provided urine samples which tested positive for opioids. Instead it was suggested that these improvements are related to an overall change in clinical status of this group when compared to their initial presentation.

Although this study failed to find any significant differences between opioid users and non substance using controls, it did show that following a period of relative stability in treatment improvements were seen in some areas of functioning. This suggested that on entering treatment, opioid dependent individuals were performing at a level below their actual optimal ability on several indices of neuropsychological functioning.

Ersche *et al.*, (2006a & 2005a) compared a group of opioid dependent individuals with a group of amphetamine dependent individuals across a number of neuropsychological domains. The opioid dependent group consisted largely of methadone maintenance patients and current illicit heroin users, as well as participants receiving prescribed buprenorphine, dihydrocodeine, diamorphine and morphine sulphate. Urine analysis showed recent use of other substances in around half of the opioid group. Control groups included drug free controls, drug free (abstinent) ex-opioid users and drug-free (abstinent) ex-amphetamine users. All participants were assessed using three measures of executive functioning (impulsivity, planning and cognitive flexibility tests) and two measures of visual memory. On the planning task, both the current and former drug users performed significantly worse than the non substance use healthy controls. Amphetamine users' performance was poorer than opioid users and there was no difference between current and former substance users. Performance on cognitive flexibility (attentional set-shift task) was comparable for all groups. On both the tests of visual memory, current and former substance users performed at a level that was significantly poorer than controls.

These results contradicted those of a number of previous and subsequent studies as it failed to find any difference between current and former heroin users. Instead these results supported the notion that the neuropsychological deficits observed in chronic opioid users were not a direct result of the opioid itself, but rather were a consequence of the factors associated with long-term drug abuse (**Darke *et al.*, 2000**). This is in contrast with more recent evidence which had provided evidence for impairments in current opioid users above and beyond those observed in abstinent ex-opioid addicts (e.g. **Mintzer *et al.*, 2005**; **Verdejo-Garcia *et al.*, 2005a, 2005b**). However there were a number of limitations to the **Ersche *et al.*, (2006a & 2005a)** study, the most obvious of these being the heterogeneous nature of the opioid group in terms of the type of opioid used, whether opioid use was illicit or prescribed opioid, and whether other illicit drugs were used concurrently. In addition, the former amphetamine and opioid users were combined into one group for comparison, with

some reporting a history of previous amphetamine use or previous opioid use and others reporting a history of both amphetamine and opioid use. Given these limitations, the results of this study should be treated with caution.

Ornstein *et al.*, (2000) conducted a study which aimed to clarify the notion that there exists a distinct profile of neuropsychological impairment which is common to heroin dependent individuals. In this study, a group of participants whose primary drug of abuse was heroin and most also treated with methadone were compared to a group who primarily used amphetamine. A third group of substance-free participants was matched to the other two groups for age and pre-morbid intellectual functioning. The assessment consisted of a number of subtests chosen from the CANTAB computerised test battery (**Sahakian *et al.*, 1988**), as well as an orally administered test of verbal fluency. These tests included measures of visual and visuospatial recognition memory, spatial working memory, attentional rule-shifting, and spatial planning. This study found that, relative to controls, the heroin group generated fewer words (but not significantly) on the verbal fluency task, and showed no improvement following practice trials on the test of visuospatial strategy. In addition, significant impairments were found in visual and visuospatial recognition memory, attentional set-shifting and spatial planning. These results pointed to the existence of a diverse pattern of neuropsychological impairment in heroin dependent individuals who were still using heroin.

Opioid users have been reported to show impairments on delay discounting tasks, where there was a steeper discounting of both hypothetical and real delayed monetary rewards (**Kirby & Petry, 2004; Bickel & Marsch, 2001**). **Rogers *et al.*, (1999a)** compared the decision making behaviour of the same sample of chronic amphetamine and opioid users in **Ornstein's *et al.*, (2000)** and compared to either healthy normal controls or a cohort with focal lesions of the orbital, dorsolateral or medial prefrontal cortex. The opioid users deliberated for significantly longer before making their decision compared to the other experimental groups who in addition also made suboptimal decisions.

Table 1.12 summarises the evidence presented in this review for an association between chronic and dependent opioid use and neuropsychological impairment.

Table 1.12: Summary of previous research regarding dependent opioid use and neuropsychological functioning.

Neuropsychological domain	Chronic opioid dependence studies*	Standardised Effect size <i>d</i> (neuropsychological test)
Cognitive Impulsivity (reflection Impulsivity)	Clark <i>et al</i> (2006)↓	0.78 (IGT) 0.68 (BIS)
Cognitive Impulsivity (risk taking)	Rogers <i>et al</i> (1999a)↓ Ersche <i>et al</i> (2005a) ↔	0.46 (CGT) 0.31 (CGT)
Motor Impulsivity (behavioural or motor response inhibition)		
Motor Impulsivity (cognitive inhibition)		
Non-Planning Impulsivity	Ersche <i>et al</i> (2006a)↓ Ornstein <i>et al</i> (2000)↓ Clark <i>et al</i> (2006)↓	0.95 (TOL) 1.18 (TOL) 0.78 (IGT)
Cognitive Flexibility (ability to shift attentional set)	Ersche <i>et al</i> (2006a)↔ Ornstein <i>et al</i> (2000)↓	0.18 (IED) 0.55 (IED)
Cognitive Flexibility (verbal fluency)	Ornstein <i>et al</i> (2000)↓	0.55 (VFT)
Sustained Attention		
Short Term Memory	Ersche <i>et al</i> (2006a)↓ Ornstein <i>et al</i> (2000)↓	0.89 (PAL) & 0.64 (PRM) 0.87 (SRM) & 0.53 (SWM)
Long Term Memory	Ersche <i>et al</i> (2006a)↓ Ornstein <i>et al</i> (2000)↓	0.98 (PRM) 0.80 (PRM)

*= $p < 0.05$; ↔= no sig. difference in neuropsychological performance; ↓= sig. neuropsychological deficits present; ↑= sig.improvement in neuropsychological performance when compared to healthy controls, *d*= Cohen's effect size defined as the difference between two means divided by a standard deviation for the data. Standardised effect sizes are reported regardless of the statistical significance (*p*-value) of the results reported in the original studies.

IGT= Iowa Gambling Task, BIS= Barrets Impulsivity Scale, VFT= Verbal Fluency Test, CANTAB: DMS=Delayed Matching to Sample Test, PAL= Paired Associate Learning Task, PRM= Pattern Recognition Memory, SRM= Spatial Recognition Memory, SWM= Spatial Working Memory, TOL = Tower of London, IED= Intra/Extra-Dimensional Set Shifting Task, CGT= Cambridge Gambling Task.

Neuropsychological functioning and dependent heroin use

Heroin (diamorphine/diacetylmorphine) is a semi-synthetic opioid which is derived from morphine. It is most often used medically as an analgesic or illicitly for recreation. Illicit heroin users will often start by 'smoking' this substance (burning the heroin and inhaling the fumes), but many will quickly progress to intravenous use. Injecting heroin allows it to pass quickly through the blood-brain barrier where it is

broken down into mono-acetylmorphine and morphine. These bind to mu-opioid receptors and result in intense analgesic, euphoric and anxiolytic effects (**Jaffe, 1990**).

Research into the effects of heroin on neuropsychological functioning is notably scarcer than the equivalent research which examines the impact of methadone. This may be because those individuals who are either currently using heroin or are completely abstinent following prior heroin dependence are less likely to be known to health services or to be currently receiving treatment. As a result they tend to be a less accessible population. However several studies have made progress in this area.

A review by **Lundqvist (2005)** discussed the research evidence for neuropsychological impairments as a result of different types of substance use. This paper concluded that 'There is a consensus that all drugs cause a disharmony in the neuropsychological network, causing a decrease in activity in areas responsible for short term memory, attention and executive functioning, with the possible exception of heroin'. However, the literature described in this section paints a different picture. Although some studies have failed to find any evidence for significant neuropsychological decline associated with heroin abuse, others have shown that individuals with current heroin use displayed impairments in a variety of neuropsychological domains. However the evidence did not support a link between the amount of heroin used and/or duration of heroin use and level of impairment (**Prosser et al., 2006**).

In Stevens *et al* (2007) tests assessing various executive functions, memory and learning were administered to 25 male heroin dependent individuals and compared to 26 polydrug abusers abstinent for more than 3 months and another 26 non substance using healthy male controls. There was significant ($p<0.05$) impairment in cognitive flexibility, working memory and sustained attention in the heroin group (**Stevens et al., 2007**).

The heroin dependent group attending a chronic pain clinic in **McNairy et al., (1984)** were significantly ($p<0.05$) impaired in verbal learning but not in memory, cognitive

flexibility and sustained attention. The study suggested that the neuropsychological impairment could have been caused by the chronic use of opioids and compounded by the 'slowed, disorganised or inappropriate responses to environmental demands for adaptive and stressful behaviour such as chronic pain and the iatrogenic prescription of opioids'.

Neuropsychological functioning in abstinent former heroin dependent populations

A number of the studies of methadone use and neuropsychological functioning included a control group of abstinent ex-heroin users (**Mintzer *et al.*, 2005; Prosser *et al.*, 2006; Clark *et al.*, 2006**), and these have generally indicated that this group may be impaired in some areas relative to controls with no history of opioid use, but may be less impaired than current methadone users. Several further studies which focused on abstinent ex-heroin users contributed to the research in this area.

Two studies by **Verdejo-Garcia *et al.*, (2007a; 2007b)** focused on the effects of substance misuse on executive functions. Specifically, these studies set out to examine executive function in abstinent polysubstance users whose primary addiction was heroin and in those whose primary addiction was cocaine. A third group of healthy, substance free controls was also included in the study. All participants in the heroin and cocaine groups had been abstinent for a minimum of two weeks and none of the participants in any of the three groups had a history of mood disorder, head injury or neurological disorder. The results showed that the heroin polysubstance users displayed significant ($p < 0.05$) impairment in motor impulsivity, cognitive impulsivity and cognitive flexibility relative to controls.

Fishbein *et al.*, (2007) contrasted the cognitive performance of four groups of participants; pure users of heroin, co-users of heroin and alcohol, pure alcohol users and non users, on measures of visual memory and different components of executive functions including, non-planning impulsivity, cognitive flexibility and cognitive impulsivity. Substance users were evaluated after three weeks of abstinence. The data suggested that heroin users had significant ($p < 0.05$) impaired performance on

cognitive impulsivity and cognitive flexibility taking more risk even though they had more time to make a decision. However performance on visual memory and problem solving tasks (non-planning impulsivity) by heroin users did better than the other two cohorts suggesting that these tasks were more closely linked to chronic alcohol rather than heroin use.

The results of this study therefore lend further support to the idea that long term heroin use cause deficits in at least some areas of executive functioning. However, because the participants included in this study were polysubstance users, it was difficult to attribute the neuropsychological impairments which were highlighted to the effects of one substance alone. It is a clinical fact that many heroin users will concurrently use a number of other substances either consistently or occasionally. This may be for a number of reasons, such as an inability to afford or obtain their drug of choice, an attempt to attenuate or alter the effect of one drug with the use of another, or because of co-existing dependencies. This prevalence of polysubstance misuse can make it difficult to identify a group of heroin users for the purposes of research. However it could be argued that including poly-substance users in this type of research will provide results which can be more easily generalised to the substance using population (**Brand *et al.*, 2008**).

A similar study by the same author (**Fishbein *et al.*, 2005a**) observed similar impairments in decision making with a group of heroin users who have been abstinent for more than 12 weeks. This heroin group selected significantly more risky choices particularly riskiest scenarios despite repeated penalties incurred (i.e. they were less likely to employ a more cautious strategy in response to improbable options). The group's choice did not appear to be due to motor impulsivity since they had ample time to think about their next move and could have been a willingness to accept the likelihood of negative consequences even in unfavourable circumstances. Such significant ($p < 0.05$) reduced cognitive impulsivity in heroin dependent individuals was suggested as a cognitive marker of substance dependence that does not recover with prolonged abstinence (**Clark *et al.*, 2006**).

In **Brand *et al.*, (2008)** eighteen inpatients from an addiction unit were tested after a two week opioid detoxification period from heroin. These opioid dependent individuals significantly ($p<0.05$) chose the risky alternatives more frequently than the control group and had struggled to shift from one perceptual set to another but performing no different in non-planning impulsivity and problem solving from the healthy non substance user control group.

Although the research in this area was limited, it seemed to point to a general improvement in at least some areas of neuropsychological functioning following at least after two week abstinence from heroin use. This suggested that some of the deficits observed in the active opioid users were either transient effects from the acute intoxication of the drug itself or that the residual impairments may be (a) permanent and a direct result of chronic opioid abuse and/or (b) factors associated with opioid abuse, and/or (c) if deficits are present they may resolve with sustained abstinence. It is therefore important to test, if there is an effect in neuropsychological performance, the same individuals prospectively at different stages of duration of abstinence.

Table 1.13: Summary of previous research regarding dependent heroin use and neuropsychological functioning.

Neuropsychological domain	Illicit chronic heroin use *	Standardised effect size <i>d</i> (neuropsychological test)	Abstinent ex-heroin use*	Standardised effect size <i>d</i> (neuropsychological test)	Chronic opioid dependence*
Cognitive Impulsivity (reflection Impulsivity)			Mintzer <i>et al</i> (2005)↓ Verdejo-Garcia <i>et al</i> (2007a)↓	0.30 (IGT) 0.54 (IGT)	Clark <i>et al</i> (2006)↓
Cognitive Impulsivity (risk taking)	Ersche <i>et al</i> (2005a)↔	0.31 (CGT)	Fishbein <i>et al</i> (2007a)↓ Fishbein <i>et al</i> (2005a)↓ Clark <i>et al</i> (2006)↓	0.38 (RDMT) 1.00 (RDMT) 0.68 (BIS)	Rogers <i>et al</i> (1999a)↓ Ersche <i>et al</i> (2005a) ↔
Motor Impulsivity (Behavioural response inhibition)		n/c	Verdejo-Garcia <i>et al</i> (2007a)↔ Verdejo-Garcia <i>et al</i> (2007b)↓	0.66 (Go-NoGo) 0.87 (Go-NoGo)	
Motor Impulsivity (cognitive Inhibition)					
Non-Planning Impulsivity			Fishbein <i>et al</i> (2007)↔ Brand <i>et al</i> (2008)↔	1.05 (SOC) 0.19 (TOH)	Ersche <i>et al</i> (2006a)↓ Ornstein <i>et al</i> (2000)↓
Cognitive Flexibility (ability to shift attentional set)	Hill & Mikhael (1979)↓ Stevens <i>et al</i> (2007)↓ McNairy <i>et al</i> (1984)↔	0.44 (CT) 0.40 (TMT) 0.18 (TMT)	Verdejo-Garcia <i>et al</i> (2007a)↓ Fishbein <i>et al</i> (2007a)↓ Brand <i>et al</i> (2008)↓	0.67 (ST) & 0.29 (WCST) 0.27 (ST) 1.42 (MCST)	Ersche <i>et al</i> (2006a)↓ Ornstein <i>et al</i> (2000)↓
Cognitive Flexibility (verbal fluency)			Prosser <i>et al</i> (2006)↔ Verdejo-Garcia <i>et al</i> (2007a)↓ Brand <i>et al</i> (2008)↔	0.33(COWAT) 0.82 (FAS) & 1.10 (RFFT) 0.52 (FAS)	Ornstein <i>et al</i> (2000)↓
Sustained Attention	McNairy <i>et al</i> (1984)↔ Stevens <i>et al</i> (2007)↓	0.20 (WAIS II) 0.32 (SRTT)	Verdejo-Garcia <i>et al</i> (2007a)↓ Mintzer <i>et al</i> (2005)↓	0.34 (5DT) 0.52 (DSST)	
Short Term Memory	McNairy <i>et al</i> (1984)↔ Stevens <i>et al</i> (2007)↔	0.21 (AVLT) 0.39 (DMS)	Verdejo-Garcia <i>et al</i> (2007a)↓ Fishbein <i>et al</i> (2007a)↔	0.81 (CBT) 0.59 (PAL)	Ersche <i>et al</i> (2006a)↓ Ornstein <i>et al</i> (2000)↔
Long Term Memory	Stevens <i>et al</i> (2007)↔	0.22 (WMSR)			Ersche <i>et al</i> (2006a)↓ Ornstein <i>et al</i> (2000)↔

*= $p < 0.05$; ↔= no difference in neuropsychological performance; ↓= neuropsychological deficits present; ↑= improvement in neuropsychological performance when compared to healthy controls, *d*= Cohen's effect size defined as the difference between two means divided by a standard deviation for the data. Standardised effect sizes are reported regardless of the statistical significance (*p*-value) of the results reported in the original studies, n/c= controls not healthy controls or not enough information to calculate effect size.

AVLT= Auditory Verbal Learning Test, BIS= Barrets Impulsivity Scale, CBT=Cognitive Bias Test, COWAT/FAS= Controlled Oral Word Association Test/Phonological Fluency Test, DSST=Digital Symbol Substitution Test, 5DT= Five Digit Test, Go-NoGo=Go-NoGo Test, IGT= Iowa Gambling Task, MCST=Maudsley Card Sorting Test, ST=Stroop Test, TOH= Tower of Hanoi, RFFT= Ruff Figural Fluency Test, SRTT=Serial Reaction Time Task, WAIS II=Wechsler Adult Intelligence Scale Second Edition, WCST= Wisconsin Card Sorting Test, WMSR= Wechsler Memory Scale Revised. CANTAB: DMS=Delayed Matching to Sample Test, PAL=Paired Associate Learning Task, TOL/SOC =Tower of London/Stockings of Cambridge, CGT/RDMT=Cambridge Gambling Task/Roger's Decision Making Test, Halstead Reitan Neuropsychological Test Battery: TMT=Trail Making Test, CT=Category Test.

Table 1.13 summarises the evidence presented in this review for an association between illicit and dependent heroin use and neuropsychological impairment at two stages of opioid receptor occupancy (use and abstinent). Overall the literature suggested limited but significant deficits in attention and cognitive flexibility in the heroin dependent population and significant deficits in attention, impulsivity and cognitive flexibility in the abstinent heroin cohorts (**Fernandez-Serrano *et al.*, 2010a, 2010b**).

Neuropsychological functioning and methadone use

Lombardo *et al.*, (1976) failed to demonstrate any difference in neuropsychological functioning as measured by the WAIS between participants maintained on 50mg and others on 80mg of methadone daily. **Gordon (1970)** and **Gorden & Appel (1995)** found no deterioration in the reaction time of methadone treated participants when compared to substance free ex-heroin users or opioid-naïve controls, even after 24 hours of methadone abstinence. Other early studies which showed minimal impairments in methadone maintenance patients (**Appel, 1982; Rothenberg *et al.*, 1977**) have been criticised for using a limited range of assessment measures (**Mintzer & Stitzer, 2002; Zacny, 1995**).

A review of these earlier studies by **Gordon & Appel (1995)** concluded that ‘there should be considerable confidence that maintenance on methadone at appropriate dosage levels, as part of treatment for heroin addiction, has little if any effect on ability to function in any capacity for which the maintained person is otherwise qualified’. However, more recent studies have in fact pointed to a wide range of possible neuropsychological deficits in methadone users.

Darke *et al.*, (2000) compared neuropsychological performance in methadone maintained individuals with opioid free controls matched for age, gender and education. This study examined a number of areas of neuropsychological functioning, including information processing, attention, short and long term verbal and non-verbal memory and cognitive flexibility. The authors reported that despite being

matched to the control group in terms of their pre-morbid level of intellectual functioning, the methadone maintenance groups' performance was significantly poorer than the control group in all domains tested. There was no significant effect of methadone dose on performance in any of the domains. However the authors pointed out that the methadone maintained group reported a significantly ($p<0.05$) higher incidence of alcohol dependence and non-fatal overdose, both of which were found to be independent predictors of poorer performance in each neuropsychological domain. The methadone maintenance group also had a significantly ($p<0.05$) higher prevalence of head injury than the control group, another common cause of neuropsychological impairment. This study demonstrated the potential difficulties in identifying neuropsychological impairment which can unequivocally be attributed to opioid abuse rather than to the range of conditions which are frequently comorbid with opioid dependency. In addition, the results of this study are limited by the fact that the methadone maintenance group reported a high incidence of other substance use, and recent illicit substance use was not objectively verified using urine analysis. The authors suggested that the neuropsychological impairments seen in opioid users are likely to be a consequence of factors associated with substance abuse lifestyle, rather than the direct effects of the opioids or other substance.

In the same year, a study by **Specka *et al.*, (2000)** also compared methadone maintained participants with matched substance free controls on a number of measures of neuropsychological functions relevant specifically to driving ability. The methadone maintained group in this study demonstrated significant ($p<0.05$) impairments in attention and tachistoscopic perception, they were faster but less accurate on a response time task (motor impulsivity deficits), and they were more accurate than controls but slower on a visual tracking test (reduced reaction time). Although this study had implications in further understanding the association between methadone and neuropsychological skills relative to driving, it was limited by the fact that participants who tested positive for other substances in their urine were not excluded.

In **2004, Rotheram-Fuller *et al.*** compared methadone maintained patients with substance free controls matched for pre-morbid intellectual functioning on cognitive impulsivity (risk taking) and cognitive flexibility (perseveration). In addition, the authors divided both groups into smokers and non-smokers in order to determine whether smoking had any impact on performance of these tasks. This study showed that the methadone maintained group who smoked displayed significant ($p<0.05$) impairments in cognitive impulsivity relative to controls and the non-smoking methadone maintained group. There were no differences between groups in cognitive flexibility. These results suggest that in addition to the numerous other risk factors for neuropsychological impairment associated with substance use, smoking may be related to impairment in cognitive impulsivity, and possibly in other neuropsychological domains.

Research conducted by **Mintzer & Stitzer (2002)**, provided evidence for the presence of impaired neuropsychological functioning as a result of methadone maintenance therapy. Their initial study in 2002 compared the performance of a group of methadone maintained participants with matched drug-free controls across a range of neuropsychological domains. Urine testing prior to assessment provided objective evidence of recent abstinence from other substances. The authors suggested that the methadone maintenance group showed significant ($p<0.05$) impairments relative to controls in the areas of psychomotor speed, short term memory, and cognitive flexibility.

In **2005, Mintzer *et al.*** developed their earlier study by comparing the results of a new group of opioid free ex-heroin users on the same battery of neuropsychological tests retrospectively with their initial two groups. The new group was matched to the earlier two groups demographically, and matched to the methadone maintenance group in terms of history of substance use. The authors found that in general the new group's scores fell between that of the methadone maintenance group and the controls on most tests, although they only performed significantly better than the

methadone group on a test of cognitive flexibility, and significantly below the control group on the task of psychomotor speed. The results of this study lent further support to the notion that the significant ($p < 0.05$) impairments seen in methadone maintained patients may be related to the direct effects of opioids rather than factors other than those associated with substance abuse (e.g. history of head injury overdose etc), as it suggested that some recovery of function may occur with detoxification from all opioids.

In a similar study, **Prosser *et al.*, (2006)** compared methadone maintained ex-heroin dependent group with a group of abstinent heroin dependent group who had been detoxified from methadone. Both groups were matched for substance using history. A group of healthy non substance using controls was also included in this study. The authors hypothesised that abstinent heroin dependent individuals should perform better than methadone maintained participants on tests of various neuropsychological skills. However, the results of this study showed that both methadone maintenance and abstinent heroin dependent groups performed significantly ($p < 0.05$) worse than controls but, at a similar level to one another, on attention and cognitive flexibility (perseveration). The only significant difference between methadone maintenance and abstinent heroin dependent groups was on a test of visuospatial memory, with abstinent heroin group performing more poorly. No effect of length or level of prior heroin use on neuropsychological functioning was found.

Although this study is useful as it compared the effects of current methadone use with the possible residual effects of long-term opioid use, caution should be used in comparing the results of the two heroin dependent groups with the non substance using healthy control group. This is because both the former groups had fewer years of formal education than controls, and their scores on a test of verbal functioning was lower than the controls. As the authors explained, this measure is often used as an estimate of an individual's pre-morbid level of intellectual functioning, suggesting that the two heroin groups had lower levels of pre-morbid intellectual functioning

than the control group. If this is the case, then it would be expected that their performance on other measures of neuropsychological functioning would also be lower, consistent with their estimated pre-morbid level of functioning. It therefore does not make sense to compare the two ex-heroin user groups with the control group in terms of test performance in order to identify impairments in the former two groups.

As the authors did not provide actual scores, it was unclear whether the two heroin dependent groups' performances were lower than would be predicted by their estimated pre-morbid intellectual functioning or at a similar level. This highlights the importance of matching controls to experimental participants in terms of estimated pre-morbid level of functioning if meaningful between-group comparisons are to be made.

Finally **Passetti *et al.*, (2008)** tested thirty seven opioid dependent heroin users six weeks after starting a community methadone treatment programme and subsequently followed up three months after. They were tested on measures of non-planning impulsivity, motor impulsivity and cognitive impulsivity (risk taking). Three months after initiation of methadone treatment, ten individuals had become abstinent for heroin while another twenty four were taking at least heroin on a weekly basis on top of their methadone medication. The study stated that performance on cognitive impulsivity (Cambridge Gambling Task and Iowa Gambling Task) at baseline could predict clinical outcome. There were no significant deficits observed in strategic planning and motor impulsivity.

Table 1.14 summarises the evidence presented in this review for an association between illicit methadone use and neuropsychological impairment.

Table 1.14: Summary of previous research regarding methadone use and neuropsychological functioning.

Neuropsychological domain	Methadone use *	Cohen's <i>d</i> (neuropsychological test)	Chronic opioid dependent use *
Cognitive Impulsivity (reflection Impulsivity)	Pirastu <i>et al</i> (2006)↓ Rotheram-Fuller <i>et al</i> (2004)↓	3.02 (IGT) 0.89 (IGT)	Clark <i>et al</i> (2006)↓
Cognitive Impulsivity (risk taking)	Passetti <i>et al</i> (2008)↓	n/c	Rogers <i>et al</i> (1999a)↓ Ersche <i>et al</i> (2005a) ↔
Motor Impulsivity (Behavioural response inhibition)	Passetti <i>et al</i> (2008)↔ Specka <i>et al</i> (2000) ↓	n/c 0.78	
Motor Impulsivity (Cognitive Inhibition)	Prosser <i>et al</i> (2008)↔		
Non-Planning Impulsivity	Passetti <i>et al</i> (2008)↔	0.98 (TOL)	Ersche <i>et al</i> (2006a)↓ Ornstein <i>et al</i> (2000)↓
Cognitive Flexibility (perseveration and attentional set shifting)	Darke <i>et al</i> (2000)↓ Mintzer <i>et al</i> (2005)↓ Rotheram-Fuller <i>et al</i> (2004)↔ Pirastu <i>et al</i> (2006)↓ Prosser <i>et al</i> (2006)↓ Soyka <i>et al</i> (2008)↓	0.65 (WCST) 0.87 (TMT) 0.61 (WCST) 7.27 (WCST) 0.65 (ST) 0.81 (TMT)	Ersche <i>et al</i> (2006a)↓ Ornstein <i>et al</i> (2000)↓
Cognitive Flexibility (verbal fluency)	Darke <i>et al</i> (2000)↓ Soyka <i>et al</i> (2008)↓ Prosser <i>et al</i> (2006)↔	0.57 (COWAT) 0.54 (RWT) 0.20 (COWAT)	Ornstein <i>et al</i> (2000)↓
Sustained Attention	Darke <i>et al</i> (2000)↓ Specka <i>et al</i> (2000)↓ Mintzer <i>et al</i> (2005)↓ Soyka <i>et al</i> (2008)↓	0.76 (WAIS II) 0.45 (DR2)& 0.64 (Q1) 1.00 (DSST) 0.77 (DR2)	
Short Term Memory	Darke <i>et al</i> (2000)↓ Mintzer <i>et al</i> (2005)↓ Prosser <i>et al</i> (2006)↓ Pirastu <i>et al</i> (2006)↓ Soyka <i>et al</i> (2008)↓	0.80 (WMSR) & 0.55 (RCFT) 0.70 (2BT) 0.97 (BVRT) 7.82 (BVRT) 0.83 (AVLT)	Ersche <i>et al</i> (2006a)↓ Ornstein <i>et al</i> (2000)↔
Long Term Memory	Darke <i>et al</i> (2000)↓	1.40 (WMSR)	Ersche <i>et al</i> (2006a)↓ Ornstein <i>et al</i> (2000)↔

*= $p < 0.05$; ↔= no difference in neuropsychological performance; ↓= neuropsychological deficits present; ↑= improvement in neuropsychological performance when compared to healthy controls, *d*= Cohen's effect size defined as the difference between two means divided by a standard deviation for the data. Standardised effect sizes are reported regardless of the statistical significance (*p*-value) of the results reported in the original studies, n/c= controls not healthy controls or not enough information to calculate effect size.

AVLT= Auditory Verbal Learning Test, BVRT= Benton Visual Retention Test, COWAT/FAS= Controlled Oral Word Association Test/Phonological Fluency Test, DSST=Digital Symbol Substitution Test, IGT= Iowa Gambling Task, , RCFT=Rey Osterreith Complex Figure Test, RWT= Regensburger Word Fluency Test, ST=Stroop Test, 2BT= Two Back Task, WAIS II=Weschler Adult Intelligence Scale Second Edition, WCST= Wisconsin Card Sorting Test, WMSR= Weschler Memory Scale Revised, CANTAB: TOL = Tower of London, Halstead Reitan Neuropsychological Test Battery: TMT= Trail Making Test, Act React Test Systems (ART 90/2020): DR2=Simple Choice Reaction, Q1= Attention under Monotonous Circumstances.

From the range of studies that have examined the impact of methadone on neuropsychological functioning there seems to be an evidence base describing impairment in methadone users in a number of neuropsychological domains. There is conflicting evidence regarding the possible impact of the dose of methadone on level of impairment with some research pointing to no effect of dose on performance, and some research reporting a dose related impact on the specific domains of delayed verbal memory and reaction time. Furthermore, other studies suggested that some recovery of functioning takes places with time in methadone maintained ex-heroin users. Finally, those studies which have compared methadone users with abstinent ex-heroin dependent and substance free healthy controls have indicated that the abstinent ex-heroin dependent group performed at a superior level to methadone users but below the level of substance free and healthy controls.

This suggested that the neuropsychological deficits observed in opioid users may be subject to at least partial recovery with total withdrawal from opioids.. However, interpretation of these results must be done with caution, as there were a number of possible causes of neuropsychological dysfunction at work in this population. These include the effects of the drug itself, as well as the effects of any other illicit or prescribed substances, alcohol abuse, the effects of previous head injury, overdose, psychiatric disorders or psychological distress. Unfortunately each confounding variable mentioned is prolific in the opioid dependent population. It is therefore likely that factors other than the direct effects of methadone account for at least some of the wide range of deficits observed in the research literature.

Neuropsychological functioning and use of other opioids.

Buprenorphine

Buprenorphine is a partial mu-receptor agonist and kappa receptor antagonist which has increasingly been used as an alternative to methadone in the treatment of opiate dependency (**British National Formulary 55, 2008**).

Soyka *et al.*, (2008) assessed the neuropsychological functioning after at least two weeks of stable substitution treatment with buprenorphine or methadone and then followed up using a repeated cognitive assessment after 8-10 weeks of stable substitution treatment. In their study, the neuropsychological battery measured attention, reaction time, verbal memory, and cognitive flexibility. Participants in both treatment modalities performed equally well at baseline in all neuropsychological domains compared to the substance free healthy control group. At follow up however there was significant ($p < 0.05$) impairment in both experimental groups in cognitive flexibility and memory when compared to the healthy control group.

In **2006**, **Pirastu *et al.*** published a study which compared a group of methadone maintained and another group of buprenorphine treated opioid dependent individuals after twelve months of treatment, with a group of substance free healthy controls. Each of the three groups included in this study were assessed using tests of cognitive flexibility, cognitive impulsivity, and verbal memory, with the aim of identifying any differences in the neuropsychological profiles of patients receiving methadone versus patients receiving buprenorphine. Participants were excluded if they had any other major risk factors for neuropsychological impairment, such as DSM-IV diagnoses of psychiatric disorder(s) (other than substance misuse disorder), serious head injury, neurological disease, psychosis, HIV, epilepsy or primary neuropsychological deficit. The results of their study showed that the buprenorphine group performed significantly better than those participants maintained on methadone and the control group in the cognitive impulsivity tasks. But both the methadone and buprenorphine groups struggled markedly on tasks measuring cognitive flexibility and memory when compared to the control groups.

Schindler *et al.*, (2004) assessed the influence of fifteen months of either methadone or buprenorphine maintenance treatment on the driving abilities of opioid dependent individuals. Using the ART 2020 Standard Test (**Bukasa *et al.*, 1997**) both experimental groups showed significant ($p<0.05$) impairment in Attention under Monotonous Circumstances Test (ACT) when compared with healthy controls. The authors postulated that this could be as a result of both experimental groups making errors to complete the task quicker, at the expense of accuracy. There were no significant differences in non-planning impulsivity, cognitive flexibility and motor impulsivity in the two groups when compared with non substance using healthy control group.

Morphine

In a long-term prospective study, **Tassain *et al.*, (2003)** evaluated the neuropsychological impact of oral sustained release morphine in participants with chronic non malignant pain. A battery of neuropsychological tests to explore attention, psychomotor speed, cognitive flexibility (verbal fluency) and memory was administered. The effects of morphine on pain, quality of life, mood, and side-effects were also investigated. Evaluations were performed at baseline to participants free from opioids and then followed up after 3, 6 and 12 months. Twenty-eight patients were included. Eighteen received oral sustained morphine (range 40–140 mg/day), ten patients stopped morphine prematurely because of side-effects or insufficient pain relief and were followed as a control group.

There was no impairment of any neuropsychological variable over time in the morphine treated group in comparison with the control. Measures of cognitive flexibility (Stroop Test) and information processing speed (Digit Symbol Test) improved at 6 and 12 months with significant ($p<0.05$) correlations with the pain relief and improvement of mood. The authors concluded that this study demonstrated that twelve months treatment with oral morphine does not disrupt cognitive functioning in patients with chronic non-malignant pain and instead results in

moderate improvement of some aspects of cognitive functioning. The authors continue by concluding that any neuropsychological improvement present was more a consequence of the pain relief and concomitant improvement of well-being and mood.

Vainio *et al.*, (1995) studied twenty four chronic morphine (mean dose of 209 mg daily) participants treated for chronic malignant pain. This cohort did not experience impairment in intelligence, motor impulsivity, cognitive flexibility (verbal fluency) and attention. The control group was an equal number of participants with malignancy who did not require opioid analgesia. Therefore this study was not tested with a substance free or healthy control group.

Combination of opioids (morphine, tramadol, fentanyl, oxycodone, buprenorphine and/or methadone)

Sjogren *et al.*, (2005) investigated the influence of pain, sedation, pain medication and sociodemographic characteristics on cognitive functioning of nineteen participants with chronic non-malignant pain prescribed morphine, tramadol, buprenorphine and/or methadone compared to sixty four healthy controls. The opioid medicated individuals identified significant ($p<0.05$) deficits in motor impulsivity but not in memory. The authors suggested that impaired sustained attention and reduced psychomotor speed in this cohort could be a consequence of high pain scores in the cohort group.

Jamison *et al.*, (2003) investigated the psychomotor effects of long-term opioid use in 144 patients with chronic non-malignant low back pain. All participants were administered the Digit Symbol and Trail Making Test-B before being prescribed opioids for pain. Tests were re-administered at 90-day and 180-day intervals. Test scores significantly ($p<0.05$) improved while participants were taking opioids for pain, which suggested that long-term opioids do not significantly impair cognitive ability or psychomotor function. Between 16% and 25% of these participants demonstrated declining performance on the individual neuropsychological tests while on opioids. In

general, those who were older and had lower pain intensity scores at their first measurement were most predisposed to poor test scores. Some participants' scores may also have changed due to situational or chance factors, variability in test administration, or concomitant treatments unrelated to opioid use or patient characteristics. The authors speculated why psychomotor performance would improve in those patients with high pain intensity. The impaired cognition in this study group compared with published standardised neuropsychological test results may be attributable to chronic pain conditions and is consistent with other findings of neuropsychological impairment in those with chronic pain (**Lorenz *et al.*, 1997; Sjogren *et al.*, 2000a, 2000b; Vainio *et al.*, 1995; Crombez *et al.*, 1996**).

Given that high pain intensity at baseline was most predictive of improvement on neuropsychological tests, it can be inferred that improvement in performance in this population was attributable to the ameliorating effects of opioids on pain rather than properties of the opioids *per se*. This was supported by the overall decrease in average pain intensity scores and SF-36 bodily pain scores between baseline and follow-up.

A number of limitations of this study deserve mention. Firstly, testing was performed in multiple sites by researchers who were not licensed psychological examiners. Thus, despite the fact that each examiner was given specific instruction on how to administer the tests and had to perform five practice test protocols, the reliability of the examiner technique was not established. Secondly, the practice effect of test taking for patients may account for some improvement in scores. The literature suggests that a 5% improvement is possible after a 3-week interval, (**Lezak, 1995**). Although this effect cannot be ruled out most participants, however, showed a better than 5% improvement on their scores. Thirdly, this study did not include a control group of patients who were not taking opioids. We do not know whether such a group followed for 6 months would also show improvement. Fourthly, approximately 30% of the participants were not followed for the full 180 days. Although no differences were found between those patients who completed the study and those who did not, it is possible that the dropouts may have biased the results. Finally, the

patients in this study were not opioid *naïve*. They may have accommodated less to the opioids and shown more cognitive impairment had they been given opioids for the first time.

Table 1.15 summarises the evidence presented in this review for an association between other opioid use and neuropsychological functioning

Table 1.15: Summary of previous research regarding other opioid (buprenorphine, morphine, oxycodone and tramadol) use and neuropsychological functioning.

Neuropsychological domain	Other opioid use *	Standardised effect size <i>d</i>	Chronic opioid dependent use *
Cognitive Impulsivity reflection impulsivity	Pirastu <i>et al</i> (2006)↑	1.94 (IGT)	Clark <i>et al</i> (2006)↓
Cognitive Impulsivity (risk taking)			Rogers <i>et al</i> (1999a)↓ Ersche <i>et al</i> (2005a) ↔
Motor Impulsivity (Behavioural or motor response inhibition)	Sjogren <i>et al</i> (2005)↓ Vainio <i>et al</i> (1995)↔ Schindler <i>et al</i> (2004)↔	n/c n/c n/c	
Motor Impulsivity (cognitive inhibition)			
Non-Planning Impulsivity	Vainio <i>et al</i> (1995)↔ Schindler <i>et al</i> (2004)↔	n/c n/c	Ersche <i>et al</i> (2006a)↓ Ornstein <i>et al</i> (2000)↓
Cognitive Flexibility (perseveration and attentional set shifting)	Pirastu <i>et al</i> (2006)↓ Soyka <i>et al</i> (2008)↓ Jamieson <i>et al</i> (2003)↑ Tassain <i>et al</i> (2003)↔ Schindler <i>et al</i> (2004)↔	5.10 (WCST) 0.78 (TMT) n/c n/c n/c	Ersche <i>et al</i> (2006a)↓ Ornstein <i>et al</i> (2000)↓
Cognitive Flexibility (verbal fluency)	Soyka <i>et al</i> (2008)↓	0.52 (RWT)	Ornstein <i>et al</i> (2000)↓
Sustained Attention	Soyka <i>et al</i> (2008)↓ Sjogren <i>et al</i> (2005)↓ Jamieson <i>et al</i> (2003)↔ Tassain <i>et al</i> (2003)↔ Vainio <i>et al</i> (1995)↔ Schindler <i>et al</i> (2004)↓	0.93 (D2) 0.36 (PASAT) n/c n/c n/c 0.57 (D2) & 0.66 (Q1)	
Short Term Memory	Pirastu <i>et al</i> (2006)↓ Soyka <i>et al</i> (2008)↓ Tassain <i>et al</i> (2003)↔	6.16 (BVRT) 3.91 (AVLT) n/c	Ersche <i>et al</i> (2006a)↓ Ornstein <i>et al</i> (2000)↔
Long Term Memory	Tassain <i>et al</i> (2003)↔	n/c	Ersche <i>et al</i> (2006a)↓ Ornstein <i>et al</i> (2000)↔

*= $p < 0.05$; ↔= no difference in neuropsychological performance; ↓=neuropsychological deficits present; ↑= improvement in neuropsychological performance when compared to healthy controls, *d*=Cohen's effect size defined as the difference between two means divided by a standard deviation for the data. Standardised effect sizes are reported regardless of the statistical significance (*p*-value) of the results reported in the original studies, n/c= controls not healthy controls or not enough information to calculate effect size.

AVLT=Auditory Verbal Learning Test, BVRT=Benton Visual Retention Test, IGT=Iowa Gambling Task, PASAT=Paced Auditory Serial Addition Task, RWT=Regensburger Word Fluency Test, WCST=Wisconsin Card Sorting Test, Halstead Reitan Neuropsychological Test Battery: TMT=Trail Making Test, Act React Test Systems (ART 90/2020): DR2=Simple Choice Reaction, Q1=Attention under Monotonous Circumstances.

Methodological issues related with the study of the neuropsychological correlates of chronic opioid use, abuse and dependence

This systematic review exploring the neuropsychological impairments associated with the chronic use of opioids highlights the need to ensure rigorous control over a number of methodological variables that may affect the reliability, validity and clinical relevance of the results obtained.

The lack of sufficient methodological rigour could be partly responsible for the lack of consistency in the results of different studies and the marked interindividual and temporal variability noted in the available literature in the field. Both the large number of variables that must be controlled, as well as the difficulties involved in their control in this type of population, present great obstacles that are difficult to surmount in the context of clinical research. In spite of the difficulties, the detection of neuropsychological impairments closely associated with substance abuse requires extreme methodological rigour and the control of the variables that have most often been associated with the discrepancies in results characteristic of research in this field (**Verdejo-Garcia *et al.*, 2004**). Among the variables that must be considered would be context, study population, substance misuse and dependence, data gathering and analysis.

Context

Considerable confusion and misleading information has arisen from many studies because of loose definitions of the terms chronicity, neuropsychology and opioids. Confusion has also arisen because many research groups, for example, only vaguely describe specific diagnostic algorithms and the degree to which they consider diagnostic exclusion rules. This is relevant whether none, some or all of the diagnostic exclusions and hierarchies have been considered. Complex sets of symptom, syndrome, and diagnostic exclusions (as employed by DSM-III-R, DSM-IV, ICD-9 and ICD-10) might all affect the result as well as their interpretation (**Wittchen, 1996**).

Further problems with defining the populations is that historically mental health, psychology and substance misuse services have evolved in their own way, using different language and models to inform their service policies and objectives (**Todd *et al.*, 2004**).

The method(s) of assessment and diagnosis may change within a country or scientific community. The settings where studies take place differ and even, if apparently similar, may not be so. Studies in one region or location may not reflect the situation in another, especially in the international context.

For studies looking at treatment seeking opioid populations it is necessary to distinguish between general psychiatric, pain and addiction services. For example, in general psychiatric services, alcohol and cannabis are more likely to be encountered as the comorbid dimension, whereas in pain and addiction services depressive, anxiety and personality disorders are going to be the additional problems most commonly reported together with opioids and cannabis being the main substance use.

The population studied

Recruitment

Recruitment related methodological problems depend largely on the type of substance abused by the target population and an important challenge in sampling is that of tracking the so-called 'hidden' population (**Heckathorn, 1997, Heckathorn, 2002**). For example, dihydrocodeine abuse has been traditionally restricted to private and erratic consumption patterns within a gainfully occupied population that rarely generate admission to treatment centres (**Shewan & Dalgarno, 2005**).

Therefore, studies tend to use the 'snowball technique', originally described by **Solowij *et al.*, (1992)**, in which subjects agreeing to participate in the study contact other acquaintances who are asked to contact other users (**Fox *et al.*, 2002; Morgan *et al.*, 2001**).

However, some other strategies have been described to recruit this population, including advertisements over the internet, in local newspapers and music magazines (**McKetin & Mattick, 1998; Thomasius *et al.*, 2003**), flyers and posters in the areas surrounding schools and universities (**Morgan, 1999; Simon & Mattick, 2002**), through word of mouth, or directly 'in vivo' on the rave scene (**Gouzoulis-Mayfrank *et al.*, 2003**). These tracking procedures introduce a methodological bias, because the subjects recruited may not be representative of the whole population of ecstasy (MDMA) users.

In contrast, opioid and cocaine users are often recruited as they join inpatient or outpatient treatment programmes (**Ornstein *et al.*, 2000; Van Gorp *et al.*, 1999**), or among the incarcerated population (**Selby & Azrin, 1998**).

Therefore, an opposite (Berkson) bias emerges, because most of the studies are unable to access those users who are not in treatment (**Berkson, 1946**). Furthermore, opioid treatment programmes may include agonist maintenance treatment with methadone and buprenorphine, introducing additional confounding factors in the detection of possible long-term effects of opioid abuse.

Therefore, different recruitment strategies would be advisable, with special emphasis on accessing the 'hidden' population of abusers to help obtain a more representative population.

Sample size

Another frequent methodological problem is that of sample size. Participants need to be matched on a series of variables (duration of abstinence, chronicity and severity of use, type of substances used), which are sometimes very difficult to control if strict methodological rigour is not observed (**Del Boca & Darkes, 2007**).

Probably for these reasons the majority of the studies that attempted to relate chronic opioid use with significant neuropsychological impairments have used small samples.

The main problem associated with using small sample sizes is the low representativity. Sample size is closely interrelated with methodological problems as a result of weak statistical power. The statistical power of a study depends on three variables: the level of significance established for the alpha level (or p value), the sample size, and the size of the effect that must be detected (**Zakzanis, 2001**).

A reduced sample size can be appropriate for detecting an average effect, but inappropriate for capturing small effects. Therefore, if the effects detected in the study of the neuropsychological correlates of chronic opioid use are of a medium size, small samples may be enough to capture them. But if, on the other hand, what we are looking for are small effects, the sample sizes that have been used would be inappropriate for their verification.

Up until now, there have been very few studies in the field that have incorporated estimations of the size of the effect. Among those that have such as **Verdejo-Garcia et al., (2007a)**, **Brand et al., (2008)** and **Fishbein et al., (2007)** used Cohen's arbitrary method of differentiating low, medium and strong effect size (**Cohen, 1977**). The systematic review in this chapter calculated the effect sizes of most identified studies showing a broad range of variation. Overall there has been a medium effect size (at least 0.45) in methadone and opioid studies but not in the heroin studies which had an overall low effect size (**Fernandez-Serrano et al., 2011**).

However, **Bezeau & Graves, (2001)** considered that this effect size is probably too small to be applied to research in clinical neuropsychology. These authors considered that, to assume the clinical usefulness of the study, it would be necessary for both populations (in this case, opioid users or dependent and controls) to be separated by

at least 0.80 typical deviations in the variable measured (**Verdejo-Garcia *et al.*, 2004; Fernandez-Serrano *et al.*, 2011**).

Substance misuse and dependence

Effects of polysubstance use

The majority of opioid-dependent participants are not users of only one substance, but rather a wide spectrum of them, so that the potentially detected neuropsychological impairments cannot really be attributed to the specific effect of the drug used. Instead, they are caused by the global effect of the group of drugs consumed (**Rounsaville *et al.*, 1982, Hay *et al.*, 2007**).

Neuropsychological research has shown that alcohol consumption is an important confounding variable in the study of the neuropsychological consequences of chronic opioid use (**Fishbein *et al.*, 2007; Darke *et al.*, 2000**). The interpretation of the neuropsychological impairments identified in chronic opioid users also seem to be frequently complicated by the high incidence of treatments with other opioids such as methadone, buprenorphine, naloxone, naltrexone, and anitdepressant, sedative and sometimes antipsychotic medications (**Ornstein *et al.*, 2000**).

In general, the studies that discriminate between the cognitive impairments attributable to the use of one isolated substance and those that are derived from effects of polysubstance use have detected a greater number of impaired functions and an increase in the magnitude of the damage among polysubstance (including nicotine dependence) user participants as well as a reduced capacity to recover these functions (**Specka *et al.*, 2000; Passeti *et al.*, 2008, Fernández-Serrano *et al.*, 2011**). However studies are too few and far between to make any conclusive remarks.

Chronicity and severity of use

The control of the chronicity and severity of the use of diverse drugs is another methodological challenge faced when studying the neuropsychological impairments associated with chronic opioid use. Some studies directly correlated both variables

with the magnitude of the neuropsychological deterioration in opioid users (**Grant *et al.*, 1978; Hill & Mikhael, 1979; Ornstein *et al.*, 2000**) whilst others have pointed out the lack of consistent relationships between the severity and chronicity of the use and the performance registered on the neuropsychological tests (**Prosser *et al.*, 2006**).

This lack of consistency probably reflects the low reliability of the self-report measures that are usually used for control and the lack of objective measurements of drug taking in the opioid users. Opioid dependent participants tend to underestimate their own levels of use (**Mensch & Kandel, 1988**) so that the data provided can skew possible correlational analyses regarding the amount of neuropsychological impairment with the levels of chronicity and severity of opioid use.

The option of carrying out toxicological urine analyses is not conclusive either. In spite of the fact that these analyses allow us to confirm the presence of a certain substance in the participants at a particular moment in time, these measures cannot be appropriate. A large quantity of information is lost about the frequency of use, the amount consumed, how recent the use was or the pattern the use has followed over a long period of time, and the results of the analyses present low correlations with the self-report measures (**Easton & Bauer, 1996**).

This could be minimised either through serial analyses of drug metabolites or utilising newer technology such as a hair analysis which have been shown to provide more definitive information about patterns of use (**Fraser *et al.*, 2002**). However these methods tend to be either not practical or prohibitively expensive.

Time window (moment of evaluation)

The moment in time of the neuropsychological evaluation is of utmost importance for an adequate detection of the impairments. If the evaluation takes place between 24 and 72 hours after the use, what we may be detecting are impairments produced by the acute (**Ersek *et al.*, 2004; Heishman *et al.*, 1996**) or withdrawal effects of the drug

(Lyvers & Yakimoff, 2003; Serper *et al.*, 2000). If evaluation takes place during the first three months of abstinence, impairments might be related to the residual effects of the drug on the participant (Ersek *et al.*, 2004; Berry *et al.*, 1993; O'Malley & Gawin, 1990).

If evaluated from the third month of abstinence onwards, the neuropsychological impairments might be associated with lasting alterations of the central nervous system that might be more stable in time and that might not revert with abstinence (Strang & Gurling, 1989; Roselli & Ardila, 1996).

It was suggested that the neuropsychological impairments resulting from substance use are partially reversible (Davis *et al.*, 2002) and that this reversibility depends on the duration of the abstinence period (Bauer, 2001; Selby *et al.*, 1995).

This systematic review shows that abstinent heroin users experience impairment in performance in decision making but it is not clear the number of functions damaged, and the magnitude of the impairments or if it is related to the length of the abstinence period; (i.e. the more prolonged the abstinence, the greater the level of recovery of these functions might be) (Pezawas *et al.*, 1998; Selby & Azrin, 1998).

Although no cut off point has been defined from which the prolongment of the abstinence is not relevant for the continuation to recover, it has been suggested that most of the neuropsychological recovery in substance misuse takes place during the first month (Goldman, 1983; Solowij *et al.*, 1995) but that superior functions or abilities like abstract reasoning or problem solving take much longer to recover, and in many cases, might never return to their premorbid levels (Ellenberg *et al.*, 1980; Gottschalk *et al.*, 2001). There is no literature to suggest that this is the same for opioid users.

Other relevant factors

Exposure to adulterants, prevalence of particular patterns of polysubstance abuse and the impact of the route of administration (e.g. injecting behaviour) all contribute to the uncertainties of attributing any observed impairment to chronic opioid use under consideration (**Carlin & Trupin, 1977; Gruber *et al.*, 2007; Lyers & Yakimoff, 2003**).

One possible solution to reduce these methodological confounders is by planning an experimental design in which:

- (a) Control groups of pure users or polydrug users who do not use the target substance, are included (**Verdejo-Garcia *et al.*, 2007a**)
- (b) Using non-substance using populations such as those with a diagnosis of chronic non- malignant pain and prescribed opioids for analgesia (**Tassain *et al.*, 2003; Vainio *et al.*, 1995**).

Data gathering (diagnostic and screening instruments)

Type of neuropsychological tests

The selection of the neuropsychological tests used should take into consideration the type of functions there is of interest in measuring, as well, as the sensitivity of these tests in detecting specific impairments in these same functions (**Lezak, 1995**).

While some studies focused on the evaluation of specific functions, mainly sustained attention and memory (**Darke *et al.*, 2000; Mintzer *et al.*, 2005; Soyka *et al.*, 2008**) and executive functioning (**Ornstein *et al.*, 2000; Rogers *et al.*, 1999a**), others carried out a more exhaustive neuropsychological evaluation (**Ersche *et al.*, 2006a, 2006b; Fishbein *et al.*, 2007; Verdejo-Garcia *et al.*, 2007a**). However, in this systematic review one finds that few studies are using the same tests, therefore making it difficult to compare the results, even when identical functions are being measured. For example in executive functioning, various authors (**Bechara *et al.*, 2000; Ornstein *et al.*, 2000; Rogers *et al.*, 1999a**) have detected impairments in cognitive flexibility and decision making in amphetamine and opiate users by using three different

instruments: Iowa Gambling Task (IGT) (**Bechara & Martin, 1994**), the CANTAB Battery (**Robbins *et al.*, 1994**), and the Rogers Decision-Making Task (RDMT) (**Rogers *et al.*, 1999a**), respectively. Further research should be conducted in order to determine the exact relationship and significance between such tests (**Monterosso *et al.*, 2001**).

On the other hand, the ecological validity of these ‘classical’ neuropsychological tests (their ability to detect impairments in functions that are adaptively relevant for the participant in their everyday endeavors), has been questioned by various authors (**Fals-Stewart *et al.*, 1994**; **Goldberg & Podell, 2000**; **Sbordone & Long, 1996**; **Verdejo-Garcia *et al.*, 2007c**), when measuring performance in decision-making, memory and attentional functions. By using these ecologically friendly paradigms, studies showed that the neuropsychological function in substance users tend to improve (**Verdejo-Garcia *et al.*, 2007c, 2007d**; **Yuille *et al.*, 1998**).

Beatty & Borrell (2000) showed that a group of drug users could perform better than a control group on a memory task in which the content of the items was adapted to the circumstances that characterized the lifestyle of the subjects. They suggested that some of the impairments detected by the ‘classical’ neuropsychological tests and attributed to prolonged substance use could be explained by the limited opportunities for knowledge acquisition imposed by their lifestyle.

Finally, one needs to be careful not to assume that tests have the predictive validity to determine who will recover from impaired neuropsychological functions and/or enhance a successful recovery process (**Passetti *et al.*, 2008**; **Fals-Stewart *et al.*, (1994)**).

Other factors to consider include the time taken to complete the tests, the order of the test presentation and the practice effects if the same tests are repeated over time (**Lowe & Rabbitt, 1998**; **Lezak, 1995**). All these factors, if not either standardised or taken into account, will influence the results.

Other potential methodological issues include the use of battery assessments instead of a succession of individual tests and deciding on the pros and cons of using computerised neuropsychological assessments instead of pen and paper assessments (**Levaux *et al.*, 2007; Ellinwood & Lee, 1997**). Some of these issues arise as a result of unstandardized presentation of stimuli and recording of responses, inefficient, inaccurate, lack of comparable collection of detailed data and lack of ecological validity between the 'classic' neuropsychological tests and computerised tests amongst others.

Defining the population

The assessment instrument used can also affect results. For example, a comparison of ICD-10 and the Composite International Diagnostic Interview (CIDI) suggests that two or three times as many psychiatric diagnoses as the clinician would assign in routine diagnostic assessment are revealed by standardised instruments (**Baldacchino & Crome, 2010**). This is particularly true for substance use disorders. Although it is not clear which of the diagnoses are really valid, it can at least be assumed that the higher comorbidity rates of the CIDI cannot be fully explained as artefactual or invalid (**Baldacchino & Crome, 2010**). There is some evidence that in the mid-1990s clinicians focused more on the current circumstances of a patient rather than the prior history of minor mental disorders since it was more likely to employ implicit hierarchies. Since most clinicians were trained at that time in traditional nosological concepts and ICD-9, they were therefore more likely to include in their diagnosis features that might justify a separate diagnosis (**Wittchen, 1996**).

Francis *et al.*, (1990) suggest that semi-structured diagnostic instruments might be more susceptible to 'halo effect' than standardised instruments. The 'halo effect' is where one characteristic or quality of an individual overshadows all other attributes (i.e. the extension of an overall impression of one particular outstanding trait to influence the total judgement and assessment of that person by an observer). **Kessler *et al.*, (1995)** demonstrated that technical modifications can significantly impact symptom reports as well as the accuracy of dating lifetime episodes of mental

disorders. Such modifications can include changes to the order in which disorders are assessed and the use of stem questions.

When conducting diagnostic interviews, reliable and consistent information is crucial. The accuracy of data provided by the patient and the stability of presenting symptoms need to be taken into account. In order to distinguish between chronologically primary and secondary disorders; age of onset, duration of symptoms as well as periods of remission and symptom offset are fundamental building blocks into which further information can be added and a fuller picture constructed. It is imperative to obtain collateral detailed information from the referring agencies, case records and significant others. This will lessen the distortion caused by intoxication, insufficient periods of abstinence on the part of participant, impaired memory, inconsistent answers, or deliberately falsified information.

Data Analysis

Most studies have been concerned with minimising Type 1 error by adjusting alpha level for multiple tests of significance (e.g. Bonferroni adjustment) (**Westfall *et al.*, 1997**). Most studies reviewed are either underpowered with no adjustment for attrition present (**Del Boca & Darkes, 2007**). Others fail to take into consideration the level and significance of the p value when multiple comparisons, such as using a family of neuropsychological tests or when multiple outcomes, are analysed (**Ioannidis, 2005**). This is further compounded by the lack of a clear hypothesis driven cohort experimental design (**Sterne and Smith, 2001**).

Conclusion

Most of the data reviewed are designed as cross-sectional studies and therefore do not allow determination whether neuropsychological impairments observed precede drug use, or, if they occur as a consequence of the effects of continued opioid use. A growing line of evidence from human studies indicates that pre-existing executive dysfunction, especially in cognitive impulsivity, may predate the onset of drug use and constitute vulnerability markers for liability to addiction (**Redish *et al.*, 2008**).

Previous literature has highlighted that illicit heroin use, methadone treatment and chronic use of other opioids could determine neuropsychological impairment in all the cognitive domains when compared with healthy non- substance using control groups. These impairments seem to improve following abstinence from opioids for at least between two and four weeks or more.

The previous literature has not only highlighted the current knowledge base on this subject but also identified methodological limitations and subsequent difficulties in interpretation what is essentially a heterogenous and non- comparable set of data.

Nevertheless the evidence from this existing literature has helped to form the basis of the hypotheses which will be examined as part of the present study in the subsequent chapters of this thesis.

Chapter 2: Methods-Chronic opioid use and neuropsychological consequences

Participants

This study employed an ambispective cohort design testing opioid exposed participants (illicit and non-illicit) and healthy non-substance using controls over a period of 24 months. Cohorts of participants with validated histories of illicit heroin use (HEROIN), stabilised methadone maintenance (METHADONE), chronic opioid prescriptions for pain (CHRONIC PAIN) and healthy controls (HEALTHY CONTROL) were recruited.

Heroin group (HEROIN)

The onset of action, peak effects, and duration of action vary with the different administration of heroin use. Patients experience heroin's effect within one or two minutes when injected intravenously and within fifteen to thirty minutes when injected intramuscularly. Heroin's peak therapeutic and toxic effects are generally reached within ten minutes when injected intravenously, within thirty minutes when injected intramuscularly or when snorted, and within ninety minutes when injected subcutaneously. Analgesic effects generally last between three and five hours (**Borg & Kreek, 1998**).

Intravenously injected heroin creates a 'rush' or a sensation of intense pleasure that begins within one minute of the injection. This 'rush' is followed by a period of sedation that lasts about an hour. The initial 'rush' is likely due to heroin's high lipid solubility and rapid penetration to the brain (**Leri, 2003**). The half-life of heroin is between fifteen and thirty minutes (**Borg & Kreek, 1998**).

The presence of impurities and additives also limits heroin absorption through mucous membranes, thus limiting its 'rush' and 'high' when it is sniffed or snorted. It will also influence the neuropsychological performance of individuals taking additives that are neurotoxic and/or psychotropic (**Schwartz, 1998**).

During the study period the mean percentage purity of illicit heroin was 40% of the total amount of the substance seized in Scotland (**EMCDDA, 2008**) and analysis of heroin seized in 2007-8 in Fife and Tayside revealed that caffeine and paracetamol were the most common added substances used to dilute the illicit heroin (**Scottish Crime Drug Enforcement Agency, 2009**). Other pharmaceutical products such as benzocaine, diazepam and phenacetin were also found in a minority of seized and analysed samples from the South East Scotland region in 2008 (**Baldacchino *et al.*, 2009**).

When heroin is discontinued, the user generally experiences physical withdrawal symptoms. Withdrawal starts within 6-8 hours of the last administration. Withdrawal symptoms include: restlessness, insomnia, diarrhoea, vomiting, cold flashes with goose bumps, kicking movements and muscle and bone pains. Major withdrawal symptoms peak between 48 and 72 hours after the last dose and subside after about a week (**DH, 2007**).

Only male participants aged between 18 and 30 years entering for the first time a structured methadone maintenance treatment programme and attending Tayside and Fife Addiction Services between January 2007 and December 2009 were considered for inclusion in this study. The potential participants had confirmed histories of more than three years of regular, daily illicit opioid (usually heroin) use and met diagnostic criteria for opioid dependence syndrome according to DSM-IV (**American Psychiatric Association, 1994; Appendix 4**).

Participants were taking between 0.4 g and 1.5g of heroin intravenously daily or smoked heroin with an equivalent daily methadone dose of 40-120mg (**Preston, 1996**) and **Table 2.1**. They were also naïve to methadone and other types of prescribed opioids. The information on the participant's drug history was subjective and there were no attempts to objectively validate the extent and magnitude of the participant's drug exposure by measuring serum levels of the opioids taken.

Measuring serum heroin and methadone levels was considered as not possible in the belief that it will increase the likelihood of attrition from the study and would have been practically be very difficult, in terms of venous access, to obtain the required two blood specimens. Also, any serum results obtained would not necessarily have provided a more accurate assessment of the optimal dosage of methadone (**Bell *et al.*, 1988**).

Table 2.1: Illicit heroin conversion chart *.

Daily spend on heroin	Amount used in grams	Route Heroin taken	Methadone dose - stabilised
£10	1/8th	Smoked	5-25mg
		IV	5-25mg
£25	0.25g	Smoked	10-40mg
		IV	15-45mg
£40	0.5g	Smoked	20-50mg
		IV	30-65mg
£50	0.75g	Smoked	30-70mg
		IV	35-75mg
£80	1.0g	Smoked	35-85mg
		IV	35-100mg
£100	1.5mg	Smoked	45-120mg
		IV	45-130mg
£150	2.0g	Smoked	50-130mg
		IV	50-130mg

*Material adapted with permission from Preston, 1996. It is not possible to accurately predict equivalent doses in most cases. This is especially true for street drugs where purity is notoriously variable. It is also problematic to convert from one drug to another when the half lives are not equivalent. Therefore this table is not intended to show absolute figures but possible range of dosages.

To standardise the pharmacological status of this HEROIN group and determine consistent stages of 'withdrawal' and optimal opioid dose a well established clinical tolerance testing procedure was used (**Appendix 5**). Tolerance testing was a single-blinded procedure that permitted the objective observation of individuals during stages of acute intoxication, withdrawal and subsequent stabilisation on a fixed dose methadone within a period of 7-14 days. Tolerance testing ensured that each participant took the dose that was considered optimal for them. Severity and quality of the opioid withdrawal symptoms were measured using the Clinical Opiate Withdrawal Scale (COWS) (**Tompkins *et al.*, 2009; Appendix 6**).

The participants were assessed on entry to tolerance testing which was between 3-5 hours after their last illicit dose so as to prevent any confounding results due to heroin intoxication. Then the same participants in the HEROIN group were invited to be retested in a state of opioid withdrawal and subsequently following a specified period of stabilisation with methadone. This assessment process took place within a 4 week period. This offered an opportunity to perform repeated neuropsychological testing during periods when illicit heroin is either present, absent or replaced by an alternative opioid (methadone) from the participant's system. This approach also determined whether any deficits present represented a stable phenomenon or could be modified by different degrees of opioid receptor occupancy.

During the study period there were a total of 635 new treatment seeking individuals aged between 18 and 30 years old. Three hundred and seventy nine individuals were males and 295 of these cases presented with an opioid dependence syndrome. Eighty seven individuals were excluded due to presence of co-morbid severe mental health and/or physical conditions and a further one hundred and thirty six individuals were excluded due to co-occurring alcohol and/or benzodiazepine dependence. Another thirty eight individuals refused to participate leaving thirty six individuals that met the study criteria and who were invited to participate in this study. In summary half of all eligible cases who attended the Dundee and Fife Addiction Services in the two year study period were approached to participate in this study.

Twenty eight (50%) of these participants consented and were tested during illicit heroin use as the HEROIN group. Twenty six of these twenty eight participants were tested after their last intake of illicit heroin and subsequently retested more than twelve hours after their last intake of illicit heroin or any other opioids (in opioid withdrawal). Twenty four of the original twenty eight participants were tested after their last intake of illicit heroin, tested again in opioid withdrawal and then finally retested three weeks after stabilised on a daily methadone dose following tolerance testing (**Appendix 7.1**). One individual died just after initiating the methadone stabilisation stage.

Methadone group (METHADONE)

Methadone is itself addictive and is only clinically prescribed for those who are clinically exhibiting physical opioid dependence especially withdrawal symptoms (**DH, 2007**). Methadone is dispensed as an oral solution (1 mg/ml) and the dose is adjusted according to the severity of the opioid dependence (**Ward et al., 1999**).

When administered at a therapeutic level to opioid dependent individuals, methadone produces no obvious psychotropic effects such as euphoria or sedation. Methadone is well absorbed when taken orally and reaches a peak plasma concentration 2-4 hours after ingestion. Methadone has a plasma elimination half life of between 18-36 hours and, for this reason, a once a daily dose of methadone is thought to induce a steady state (**Curran et al., 2001**).

All male opioid dependent individuals aged between 18 and 30 years on methadone maintenance programme for more than 6 months, who showed retrospective and regular objective confirmation of the absence of illicit drug through weekly urine drug screen analysis and attending Fife Addiction Services between January 2007 and December 2009 were considered for inclusion in this study.

The potential participants had confirmed histories of more than three years of regular, daily illicit opioid (usually heroin) use and met a diagnosis of opioid dependence syndrome according to DSM-IV (**APA, 1994**). The participants have been taking between 0.4 g and 1.5 g of heroin intravenously daily or to have smoked heroin such that they have achieved a similar degree of drug exposure and clinically translating itself to an equivalent daily methadone dose of 40-120mg (**Preston, 1996**). During the study period there were 2344 treatment seeking individuals who presented with opioid dependence and were prescribed methadone in Fife. One thousand five hundred and thirty four individuals were males with 524 of these individuals aged between 18 and 30 years old. Two hundred and ninety four individuals resided in Central Fife which included the Kirkaldy and Levenmouth areas. One hundred and seventy four of these opioid dependent individuals were excluded

due to the presence of co-morbid severe mental health and/or physical conditions and co-occurring alcohol and/or benzodiazepine dependence. Another seventy eight individuals were excluded since they did not show stability as stipulated by the study protocol. Overall forty two individuals fitted the inclusion criteria for the METHADONE group and were approached to participate in this study. Twenty nine (69%) agreed to participate and consented (**Appendix 7.2**).

Throughout the study period, participants were asked to take their prescribed dose of methadone in the morning (8-10am) so that this allowed testing to happen about four hours afterwards (2-5pm). This created a standardised approach to the timing of methadone intake and neuropsychological testing. The mean daily dose of methadone varied but was within the 40-120 mg range with a morphine equivalent mean of 147.41 (+/- 59.33) mg daily if we assume that the heroin purity of the samples used by the participants was 40%.

In order to determine that the results obtained were not time specific to the episode of treatment, eighteen out of the twenty nine participants were evaluated prospectively six months after their baseline neuropsychological test session.

Chronic pain group (CHRONIC PAIN)

All male non- opioid dependent individuals aged between 18 and 40 years with a history of more than three years of continuous prescribed opioids and attending the Tayside Pain Clinic between January 2007 and December 2009 were considered for inclusion in this study.

The potential participants had no history of 'illicit' opioid (e.g. heroin) use or methadone treatment and would not have met the criteria for a diagnosis of opioid dependence syndrome according to DSM-IV (**APA, 1994**).

During the study period there were a total of 303 treatment seeking individuals aged between 18 and 40 years who were referred to the Tayside Chronic Pain Clinic based

at Ninewells Hospital and Medical School in Dundee. Forty one individuals who had a history of opioid medication for more than three years due to chronic non--malignant pain were approached to participate in this study. On further assessment three of these cases did not fit the eligibility criteria due to (a) one case having a recent diagnosis of malignancy, (b) one case leaving the catchment area and (c) another stopping his opioid medication due to an improvement in his chronic painful condition. In total twenty eight (72%) eligible individuals were approached and they all consented to participate (**Appendix 7.3**).

Normal control group (HEALTHY CONTROL)

The control group consisted of twenty eight healthy males matched for age and sex, with no history of chronic pain and/or illicit drug use or a lifetime continuous/regular prescription of opioids. This group were recruited from the general population residing in Fife and aged between 18 and 40 years.

General study design

The study design created an experimental model within which individuals either experienced different degrees of opioid receptor occupancy (HEROIN) or were receipt of chronic and stable prescribed opioids (METHADONE and CHRONIC PAIN).

Further, by including a cohort of non-heroin abusing individuals (CHRONIC PAIN) recruited from a pain clinic, one was able to identify the possible effects of drug adulterants and/or the 'drug addict lifestyle'. By including a cohort of stable methadone maintained individuals (METHADONE) one was also able to retrospectively identify the possible contamination effect of previous illicit heroin use and prospectively test for deterioration and/or improvement.

The HEROIN group performed the neuropsychological tasks between three and five hours after smoking or injecting illicit heroin (baseline). They were then re-tested when experiencing opioid withdrawals ten to fifteen hours after stopping any opioid use as part of a tolerance testing procedure. This cohort was again re-tested between

two and four weeks after the tolerance testing procedure when this cohort was adequately stabilised on a daily dose of methadone. They were therefore tested on three occasions.

The METHADONE group performed the neuropsychological tasks between 4-6 hours of taking their last stable dose of methadone (baseline). They were re-tested again six months after their initial baseline test period. They were therefore tested on two occasions.

The CHRONIC PAIN group performed the neuropsychological tasks between 4-6 hours after taking their chronic stable dose of opioid medication. They were therefore only tested at baseline.

The HEALTHY CONTROL group was tested once at baseline (**Table 2.2**).

Table 2.2: Study procedures.

Testing Sessions	Illicit or licit opioids	Opioid withdrawal	2-4 weeks on methadone	6 months on methadone
HEROIN	†	†	†	—
CHRONIC PAIN	†	—	—	—
METHADONE	†	—	—	†
HEALTHY CONTROL	—	—	—	—

†= tested; —= not tested

A two staged screening and assessment process was used. The identified individuals were approached by their keyworkers in order to seek interest in participation to this study. Informed written consent to participate in the study was obtained from this group in accordance with the guidelines from the Tayside Committee on Medical Research Ethics. Consent was subsequently obtained after the first meeting with the researcher (**Appendices 8 & 9**).

Inclusion and exclusion criteria

Criteria for inclusion and exclusion to this study was based on the methodological limitations and confounding factors identified in Chapter 1.

The inclusion criteria were:

- Male gender
- Males older than 18 years and younger than 30 years. In the CHRONIC PAIN and HEALTHY CONTROL groups the age limit was increased to 40 years.
- Presenting with opioid dependence syndrome in the drug using population (HEROIN and METHADONE groups) and not in the CHRONIC PAIN group,
- More than three years of daily opioid use.

All individuals who presented with the following conditions were excluded. They were:

- Female gender.
- Males younger than 18 years and older than 30 years in the METHADONE and HEROIN groups only.
- Intoxication due to drug and/or alcohol use.
- Co-occurring severe physical problems with acute confusional state.
- Presenting with opioid dependence syndrome in the chronic pain group.
- Co-occurring benzodiazepine, psycho-stimulant and alcohol dependence.
- History of Acquired Immunodeficiency Syndrome (AIDS) or associated HIV infection.
- Post Trauma Amnesia.
- Recent and past overdose episodes needing Cardio Pulmonary Resuscitation (CPR).
- Bipolar or severe depressive mood disorder.
- Schizophrenia.
- Post Traumatic Stress Disorder (PTSD).
- Attention Deficit Hyperactivity Disorder (ADHD) (Adult and Childhood).
- History of confirmed epilepsy.

- Neurological (sensory and motor) impairment.
- Previously determined learning disability (Intelligence Quotient (IQ) lower than 80).
- Inability to understand English.

Screening clinical instruments

Eligible and consented individuals were then screened using a battery of validated instruments and their psychiatric, addiction and general practice case records accessed.

The screening clinical instruments included the Mini International Neuropsychiatric Interview (MINI) (**Sheehan *et al.*, 1998**) and Post Trauma Questionnaire (PTQ) (**McMillan *et al.*, 1996**) (**Appendices 10 & 11**).

A drug urine analysis screen was also conducted to validate a three or four day history of opioid (usually heroin) intake and also absence of any other illicit drugs such as amphetamine, cocaine, benzodiazepine and cannabis (**Quantum Diagnostics Ltd**) as part of the screening process.

Assessing and screening for mental health related problems/illnesses: Mini International Neuropsychiatric Instrument (MINI) version 5.0

The M.I.N.I. is a brief structured diagnostic and screening interview for the major Axis I psychiatric disorders in DSM-IV and ICD-10 (**Sheehan *et al.*, 1998**). Validation and reliability studies have been done comparing the M.I.N.I. to the Structured Clinical Interview for DSM III-R Patients (SCID-P) and the Composite International Diagnostic Interview (CIDI) with results showing that the M.I.N.I. has acceptably high validity and reliability scores (**Sheehan *et al.*, 1997**).

It elicits all the symptoms listed in the symptom criteria for DSM-IV and ICD-10 for 15 major Axis 1 diagnostic categories, one Axis II disorder. It uses a decision tree logic which is consistent with DSM-IV and ICD-10 diagnostic algorithms. The MINI includes

a psychiatric assessment of current diagnoses of PTSD, panic disorder, generalized anxiety disorder, social phobia, major depression, psychotic disorders, substance (drug and alcohol) abuse or dependence, ADHD, antisocial personality, somatisation and adjustment disorders (**Sheehan *et al.*, 1998**).

With an administration time of approximately 15 minutes, the M.I.N.I. is the structured psychiatric interview of choice for psychiatric evaluation and outcome tracking in clinical psychopharmacology trials and epidemiological studies. Participants' views of MINI were also positive (**Amorin *et al.*, 1998**). It was considered comprehensive enough to cover all patient symptoms and at the same time not being unduly lengthy.

Assessing and screening for episodes of head injury and other cerebral insults: Post Traumatic Amnesia Questionnaire (PTQ)

Post-Traumatic Amnesia Questionnaire was considered to be the best single indicator of the severity of closed head injury (**Russell & Smith, 1961**). The duration of post-traumatic amnesia was taken to be the interval between injury and the patient regaining continuous memory for day to day events. The interview was structured by using notes in case records and dates of special events (**Appendix 11**) to establish landmarks in the acute stage after the head injury (**McMillan *et al.*, 1996**).

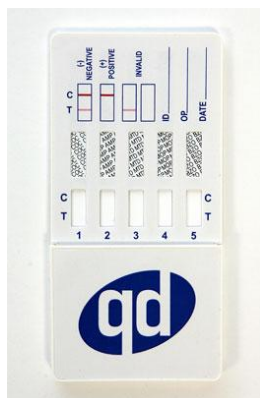
Objective measurement of substance misuse: urine analysis drug screening method

Recent substance use may result in symptoms that are indistinguishable from psychiatric symptoms. Accurate interpretation of the screening tests within a clinical setting, alongside other relevant information, remains the key to the usefulness of any test (**Simpson *et al.*, 1997; Neale & Robertson, 2003**).

Quantitative accuracy usually demands the collection of a blood, hair or saliva samples. The advantage of hair sampling is its reflection of weeks/months rather than hours of recent use (**Wolff *et al.*, 1999**). All the above tests are expensive and analysis of urine is currently the biological tool of choice for qualitative detection of illicit drug

use, becoming a common objective adjunct in the validation and reliability of substance misuse and mental health screening and/or diagnostic instruments (**Wolff *et al.*, 1999**). The significant advantage of urine for drug testing is that biologically urine is generally available in sufficient quantity and the drugs or their metabolites tend to be present in relatively high concentrations (**Moffat *et al.*, 1986**).

The procedure used in this study was for analysis for drugs of misuse undergoing an initial screening test using self-contained drug testing kits for on-site testing (**Armbruster & Krolak, 1992; Jenkins *et al.*, 1995**). The kit testing for cannabis, opioids, benzodiazepine, amphetamine and cocaine onsite was used for this study (**Quantum Diagnostics Ltd** and Illustration below).



The same urine sample were then sent to the laboratory for another screening process using an automated Enzyme-Mediated Immunoassay (EMIT) or Enzyme Linked Immunosorbent Assay (ELISA) to classify the type of drug (i.e. opioid, benzodiazepine, etc.) (**Wilson *et al.*, 1994**). In the event of a positive finding a thin-layer (TLC), gas (GC) or liquid (LC) chromatography would be used for confirmation of a specific drug in the sample (i.e. morphine, codeine etc) (**Braithwaite *et al.*, 1995; Simpson *et al.*, 1997**).

Diagnostic clinical instruments

The diagnostic clinical instruments used for this study include the MINI (**Sheehan *et al.*, 1998**), the Maudsley Addiction Profile (MAP) (**Marsden *et al.*, 1998a & 1998b**), and the Fagerström Test for Nicotine Dependence (FTND) (**Fagerström & Schneider, 1989**) (**Appendices 12 & 13**). Drug urine samples to confirm a recent history of opioid (heroin) intake and absence of any other illicit drugs. (**Quantum Diagnostics Ltd**) were analysed throughout the study period from all cohorts participating including the HEALTHY CONTROL group. The Clinical Opiate Withdrawal Scale (COWS) quantified the level of opioid withdrawal in the HEROIN group.

Assessing diagnosis of opioid dependence syndrome: Mini International Neuropsychiatric Instrument (MINI) version 5.0

The MINI is a brief structured diagnostic and screening interview for the major Axis I psychiatric disorders in DSM-IV and ICD-10 (**Sheehan *et al.*, 1998**). Description of the MINI is provided in the previous section. Diagnosis of opioid dependence, use and abuse (lifetime and current) was possible using the MINI (Section L) (**Appendix 10**).

Assessing diagnosis of substance misuse problems: Maudsley Addiction Profile (MAP)

The MAP is a brief, multi-dimensional tool designed for assessing treatment outcome (**Marsden *et al.*, 1998a, 1998b**). The MAP was developed from the interview instrument used in the National Treatment Outcome Research Study (NTORS) (**Gossop *et al.*, 1997**). It was originally designed as a core research instrument to be used by treatment services wishing to undertake outcome studies.

The MAP employs a simple scoring system in each of the four domains incorporating continuous measures or 'Likert' type severity of symptom/condition. It covers four main domains: substance use, health risk behaviour, physical and psychological health and personal/social functioning of the last 30 day period. It is interviewer administered and has 60 items in these four domains and takes about 15 minutes to complete.

The positive features include that it is quick and easy to complete, has good evaluation data and records the participants' views/opinions. A validation study showed that the content of MAP was acceptable to participants (**Marsden *et al.*, 1998a, 1998b**). Further, internal reliability and feasible concurrent validity assessments of the scales and items were highly satisfactory. Test-retest reliability was good, average intra-class correlation coefficients across eight substances were 0.94 and 0.81 across health risk, health problems, relationship conflict, employment and crime measures (**Marsden *et al.*, 1998a, 1998b**).

Assessing diagnosis of nicotine dependence: Fagerström Test for Nicotine Dependence (FTND)

The Fagerström Tolerance Questionnaire (FTQ), developed in 1978 (**Fagerström, 1978**), was widely used in smoking research (**Fagerström & Schneider, 1989**) but revealed unacceptable internal consistency (**Pomerleau *et al.*, 1994** & **Swan *et al.*, 1991**). In response to this, **Heatherton *et al.* (1991)** revised the FTQ and developed a scale called Fagerström Test for Nicotine Dependence (FTND) (**Appendix 13**).

Since 1991, the FTND is one of the most widely accepted evaluative instruments to establish and quantify nicotine dependence and also has been found to be reliable and valid in several different contexts (**Dijkstra & Tromp, 2002; Etter, 2005**). Studies have also evaluated the factor structure of the FTND among different types of population (**Radzius *et al.*, 2003; Vink *et al.*, 2005; Haddock *et al.*, 1999**).

The Fagerström Test for Nicotine Dependence (FTND) consists of six items from original FTQ, has a score range from 0 to 10 with an internal consistency of = 0.61 (**Heatherton *et al.*, 1991**). It is a self reporting tool that conceptualizes dependence through physiological and behavioural symptoms. It requires a few minutes to complete.

All participants were tested approximately one hour after their last nicotine intake and were encouraged to smoke again if the neuropsychological testing lasted more than two hours in order to prevent changes in nicotine levels influencing the test outcomes.

Assessing diagnosis of opiate withdrawal: Clinical Opiate Withdrawal Scale (COWS)

The COWS is a clinician-administered, pen and paper instrument that rates eleven common opiate withdrawal signs or symptoms (**Appendix 6**). A total score of 5 to 12 is indicative of mild withdrawal; 13 to 24, moderate withdrawal; 25 to 36, moderately severe withdrawal; and > 36, severe withdrawal. The summed score of these eleven items can be used to assess a patient's level of opiate withdrawal and to make

inferences about their level of physical dependence on opioids (**Wesson & Ling, 2003**). The COWS can be administered serially to identify changes in the severity of the signs and symptoms of opiate withdrawal.

COWS has shown strong discriminant and concurrent validation and reliability ($\alpha=0.78$) when compared to the Clinical Institute Narcotic Assessment (CINA) scale and Visual Analogue Scale (VAS) (**Tompkins *et al.*, 2009**).

Table 2.3: Summary of screening and diagnostic clinical instruments and their measures/domains.

Screening Tests	Measures/Domains
Mini International Neuropsychiatric Instrument (MINI) v5.0.	Diagnosis of 15 Axis 1 and 1 Axis 2 DSM-4 psychiatric illnesses and substance misuse/dependence presented in 24 modules.
Case records from addiction, psychiatric and General Practitioner's Services.	Identification of non fatal overdose episodes Confirming a history or not of epilepsy and other neurological phenomenon including learning disabilities. Confirming a diagnosis of Hepatitis B, C and HIV Validating medical and psychiatric histories Validating substance misuse career and current drug and alcohol use. Scottish Index of Multiple Deprivation (SIMD).
Post Trauma Amnesia Questionnaire v1.0.	Information on head and other cerebral insults and consequential post trauma amnesia.
Urine analysis for drug screen.	Using self contained on site drug test kits for presence of amphetamine, cannabinoids, opioids, benzodiazepine and cocaine. Subsequent lab investigations used ELISA followed up by TLC methodologies.
Diagnostic Tests	Measures/Domains
Mini International Neuropsychiatric Instrument (MINI) (Section L) v5.0.	Diagnosis of opioid misuse/dependence (lifetime and current).
Maudsley Addiction Profile (MAP) v1.0.	Information on substance misuse history, health risk behaviour, physical and psychological health, personal and social functioning in the last 30 days.
Fagerström Test for Nicotine Dependence (FTND) v1.0.	6 items with a diagnostic score ranging from 0 (no nicotine dependence) to 10 (very severe nicotine dependence).
Clinical Opiate Withdrawal Scale (COWS) v1.0.	11 objective and subjective symptoms of opioid withdrawal. Scores ranged from 0-48.
Urine analysis for drug screen.	Using self contained on site drug test kit for presence of amphetamine, cannabinoids, opioids, benzodiazepine and cocaine. Subsequent lab investigations used ELISA followed up by TLC methodologies.

In summary the decision to choose the above screening and diagnostic clinical instruments were made due to a combination of:

- It took a maximum of 45-60 minutes to complete all the questionnaires
- The questionnaires used were valid and reliable instruments within the population tested
- All the questionnaires used were free with no need for specialised training
- The questionnaires were user friendly and easy to administer
- The questionnaires helped differentiate co-morbid situations quickly
- The scoring methods were easy to use and interpret
- The questionnaires provided feedback to the participants on their performance

Diagnostic neuropsychological tests

Testing pre-morbid intelligence

The National Adult Reading Test (NART) (**Nelson & O'Connell, 1978; Nelson, 1982**) was used to estimate general intellectual ability for all three experimental groups and control participants. The NART assesses pre-morbid crystallised intelligence and was chosen for its ease of administration and ability to be used with individuals experiencing organic conditions including substance misuse related problems (**Crawford *et al.*, 1988a**). The NART score correlates significantly with education ($r=.51$) and social class ($r=.36$) (**Crawford *et al.*, 1988b**) with no gender effects (**Schlosser & Iverson, 1989**). It consists of 50 phonetically irregular English words whose proper reading depends on the previous knowledge of the subject rather than on phonological decoding skills.

CANTAB neuropsychological tasks

The neuropsychological tasks were selected from the Cambridge Neuropsychological Test Automated Battery (CANTAB) (**Morris *et al.*, 1987**). CANTAB is a computer-administered, non-verbal (visually presented) set of tasks developed to examine specific components of cognition, particularly those associated with frontal and medial temporal regions of the brain (**Robbins *et al.*, 1994; Robbins *et al.*, 1998**). The

particular strength of the CANTAB battery was that it incorporates a wide variety of executive and memory tasks selected on the basis of adaptations for use with humans on paradigms developed from animal models with damage to specific brain areas (**Lowe & Rabbit, 1998**). CANTAB has been used with a wide variety of populations including substance misusers and psychiatric patients, with varying levels in ability, intellect and age (**Rogers *et al.*, 1999a; Ornstein *et al.*, 2000; Fox *et al.*, 2002; Elliot *et al.*, 1998; Goodwin & Clark, 2002**). The graded nature of the tasks reduced the likelihood of floor and ceiling effects (**Fray & Robbins, 1996**). Critics of CANTAB argued that its strength centred on being exclusively non- verbal in its response requirement and in the nature of the stimulus presentation which could limit conclusions that can be drawn about the participant's verbal functioning (**Luciana, 2003**). In addition the ecological validity of CANTAB needed further investigation in order to establish the value of CANTAB tests outcomes as predictors of community functioning and levels of morbidities within the population studied (**Levaux *et al.*, 2007**). The CANTAB tests were considered suitable for this study since they tested all neuropsychological domains identified as important in the population to be studied allowing adequate comparison with results and conclusions from previous literature.

At the beginning of the testing session participants were shown a line marked on the table to which they were instructed to keep their 'pointing' finger on at the beginning of each test and between trials. This line was measured as 12 inches from the centre of the screen. The instructions given for each task originated from manuals provided by CENES (**Cambridge Cognition**), the company responsible for commercial development and marketing of the CANTAB tests. The product used for this study was CANTAB eclipse version 3.

Nine tests (and two screening tests) from three out of the four CANTAB battery neuropsychological domains were used in this study. These were: (1) executive function; (2) decision making and response control; (3) visual memory, These tests were presented on a high-resolution colour monitor with a touch sensitive screen and

run on standard Windows based PC systems. The neuropsychological tests were grouped in the same domains established in Chapter 1:

- (1) Induction stage: Motor Screening Test (MOT) and Big/Little Circle (BLC).
- (2) Cognitive Impulsivity: Cambridge Gambling Task (CGT).
- (3) Motor Impulsivity: Affective Go-NoGo (AGN);
- (4) Non-planning Impulsivity (Strategic Planning): Stockings of Cambridge (SOC); Spatial Span (SSP); Spatial Working Memory (SWM).
- (5) Cognitive Flexibility: Intra/Extra-Dimensional Set Shifting (IED).
- (6) Memory and Learning: Delayed Matching to Sample (DMS); Paired Associates Learning (PAL); Pattern Recognition Memory (PRM); Spatial Recognition Memory (SRM).

Induction (screening) stage

Motor Screening Test (MOT)

This simple reaction time test measured psychomotor speed and accuracy and was designed to screen for psychomotor impairments, which would interfere with later task performance. On each of ten trials, a large 'X' appeared at a random location on the computer screen. Participants had to touch the centre of the 'X' as quickly but as accurately as possible. Accuracy of touch and response latency was recorded. All participants were deemed to understand this task. Hence, data from this task were not analysed in any detail and are not discussed further.

Big/Little Circle (BLC)

The purpose of this simple discrimination task was to ensure participants can reliably choose between two stimuli according to a simple rule before progressing to a more complex task which was the IED. Participants were presented with two filled, yellow circles displayed in boxes. One circle was small (described during the task as 'little') in size and one big in size. In the first twenty trials, subjects were instructed to touch the 'little' circle each time, and in a second set the 'big' circle each time (**Figure 2.1**). The task took three minutes to complete. Accuracy of response and speed of response was recorded as outcome measures. All participants were deemed to understand this

task after the second twenty trials. Hence, data from this task were not analysed in any detail and are not discussed further.

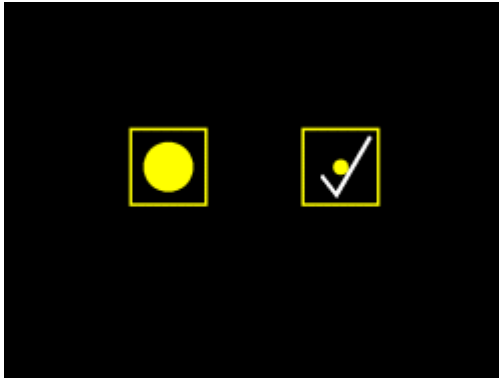


Figure 2.1: CANTAB and Big Little Circle (BLC). In the first 20 trials, subjects were instructed to touch the 'little' circle each time.

Cognitive Impulsivity

Cambridge Gambling Task (CGT)

The Cambridge Gambling Task (CGT) is a computerized measure of risky decision making but with less emphasis on strategy and working memory than the Iowa Gambling Task (IGT) (**Rogers *et al.*, 1999a & 1999b**). Unlike other 'gambling' tasks, CGT was developed to permit the separation of components that underlie cognitive impulsivity, i.e. sensitivity to consequences and risk taking outside a learning context (**Manes *et al.*, 2002**). Relevant information was presented to the participant 'up-front' and there was no need to learn or retrieve information over consecutive trials.

Brain injury, alcoholism and drug abuse were all conditions sensitive to this test. Previous studies have shown performance of individuals with a drug addiction to be characterised by sub-optimal decisions and/or slower speed of decision-making (**Rogers & Robbins, 2001**). The likely neural substrate for this task was the orbito-frontal prefrontal cortex (OF-PFC) (**Ersche *et al.*, 2011**).

On each trial, the participant was presented with a row of ten boxes across the top of the screen, some of which were red and some of which were blue (**Figure 2.2**). At the bottom of the screen were rectangles containing the words 'Red' and 'Blue'. The

participant was asked to guess whether a yellow token was hidden in a red box or a blue box.

In the gambling stages, participants started with a number of points, displayed on the screen, and selected a proportion of these points (displayed in either rising or falling order) in a second box on the screen, to gamble on their confidence in this judgement. A stake box on the screen displayed the current amount of the bet (**Figure 2.2**). The participants were asked try to accumulate as many points as possible.

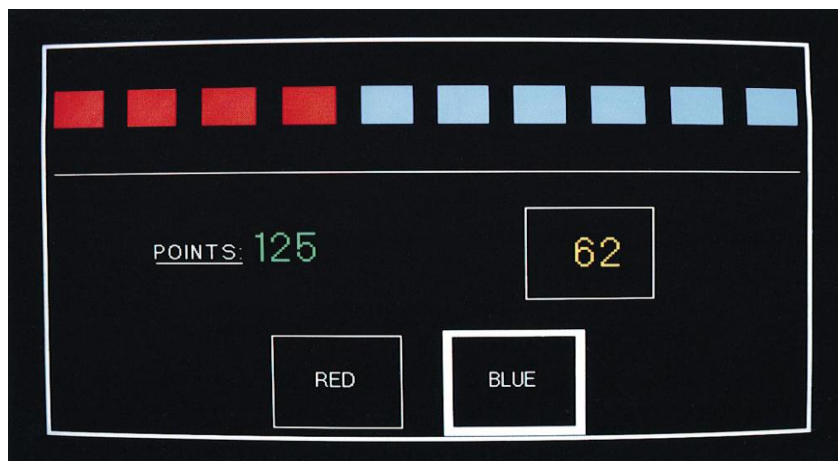


Figure 2.2: CANTAB and CGT: a typical display from the decision-making task.

The ratio of coloured boxes varied across trials. This helped examine a participant's decision-making behaviour over a variety of differentially weighted contingencies (difficulty levels). On each trial, the participant was asked to guess which colour concealed a token, and then wager a proportion of his/her total points on his/her colour decision. Thus, a participant's choice of contingency, speed of choice, and size of bet were expected to differ as a function of the ratio of red/blue boxes.

Wagers were offered in ascending (5%, 25%, 50%, 75%, and 95% of current points) or descending (95%, 75%, 50%, 25%, 5% of current points) sequences presented for 2.5 seconds each. This afforded the possibility of isolating merely impulsive behaviour from genuine risk seeking. In both ascending and descending conditions, each bet was presented with a short tone whose pitch corresponded to the size of bet: higher

tones accompanied larger bets and lower tones accompanied small bets. If the participant failed to select a bet by the end of a sequence, the last bet was chosen automatically.

Immediately following such a selection, one of the red or blue boxes opened to reveal the location of the token, accompanied by either a 'You win!' message and a short rising musical scale, or a 'You lose!' message and a low tone. If the participant chose the correct colour, the bet placed was added to the total points score; if the participant chose the wrong colour, the bet was subtracted.

On 80% of trials the probabilities were unequal and the large reward was always associated with the least likely outcome. Participants then had to decide whether to play safe and choose the likely option, which was associated with a small reward, or whether to take a risk and select the unlikely option, which was associated with a large reward. However, playing safe did not imply the participant was guaranteed to receive reward, since on 1/4 of trials the likely small reward option did result in loss. This assessed participant's willingness to place already-accumulated reinforcement at risk in the hope of acquiring more reward. For example, one might suppose that a ratio of 9 red : 1 blue represented an opportunity to bet more points on a red decision in order to gain more reward, while a ratio of 6 blue : 4 red represented a situation in which more conservative behaviour might be appropriate.

These bet options were presented sequentially in either ascending or descending order; in half of the games the ascending condition was used, and in half the descending condition. Participants played eight games each consisting of nine trials. The participant was instructed to treat the points as being valuable and to accumulate as many as possible during the test. However, no monetary significance was attached to the total points accumulated by the end of the task.

Participants simply won or lost the amount of points they chose to bet on each trial. Thus, consistently choosing the least likely outcome in this task indicated *poor quality*

of decision-making. Previous literature have determined a cut off score that appeared to discriminate between substance dependent individuals and individuals without dependency (**Bechara & Damasio, 2002**). A quality of decision making score of 89.7% for the CGT (**Rogers et al., 1999a**) is usually used as the cut of point for the CGT.

Risk taking (or overall proportion bet) on this task was characterized by choosing the least likely choice in pursuit of a greater reward even in the face of a more likely penalty.

Other outcome measures covered were *deliberation time or latency* needed to make the colour choice (**Deakin et al., 2004a, 2004b**), *delay aversion or insensitivity to cues* when the participant is unwilling to wait, betting larger amounts when the possible bet amounts were presented in descending order than they do when the amounts were presented in ascending order and *risk adjustment or lack of risk insight* when the participant has a tendency to bet a higher proportion of their points on a trial if the odds were strongly on one's favour.

Motor Impulsivity

Affective Go-NoGo (AGN)

This task was modelled on the 'set-shifting' paradigm of **Dias et al., (1996)**, and the 'modified affective shifting' task developed by **Murphy et al., (1999)**. It is an adaptation of the classic Go-NoGo paradigm that has been used for decades to test behavioural inhibition in both animals (**Mishkin & Pribram, 1955**) and humans (**Costantini & Hoving, 1973**). The emotional Go-NoGo task yields the same measure of inhibition, but the substitution of affective stimuli instead of the letters or pictorial stimuli used as Go and NoGo cues also permitted analysis of performance in response to cues of different emotional valences (e.g. happy versus sad). Therefore, the task not only provided a measure of behavioural inhibition, but also of the emotional modulation of this inhibition (**Drevets & Raichle, 1998**).

Neuroimaging studies with this task implicated the subgenual and rostral anterior regions of the cingulate gyrus in these emotional response biases (**Elliott *et al.*, 2000; Elliott *et al.*, 2002 & Elliott *et al.*, 2004**). These studies also found activation of lateral orbitofrontal cortex when inhibiting responses to NoGo cues of any valence. Another study of healthy adults that used a Go-NoGo task with affective facial expressions as cues found slowed responses to fearful expressions that were associated with amygdala activation and difficulty inhibiting responses to happy faces that was inversely related to caudate nucleus activity (**Hare *et al.*, 2005**). This study also noted consistent activation of a prefrontal region near the lateral orbitofrontal cortex during the inhibition of responses to NoGo cues regardless of emotional valence.

In the Affective Go-NoGo task, words were rapidly presented one by one in the centre of a 12-inch black screen. Words were shown as 8-mm white letters (**Figure 2.3**). Participants responded to targets by pressing the space bar with their dominant hand as quickly as possible and not responding when ‘distractors’ appear.



Figure 2.3: CANTAB and AGN. A happy valenced word presented.

The task consisted of ten word blocks, each containing 18 affectively valenced words (nine happy, nine sad), each of which presented a series of words from two of three different affective categories: In this task positive/happy (H) (e.g. joyful), and negative/sad (S) (e.g. hopeless) but not neutral (N) (e.g. element) words were chosen.

The participant was instructed initially to press the space bar when they saw a happy word (e.g. hopeful, serene) but not for sad words (e.g., glum, mistake). After two 18-

word blocks requiring responses to happy words, the participant was then instructed to respond (press space bar) when he/she saw a sad word (e.g. glum). The presentation of valenced words alternated every two blocks and continued for ten 18-word blocks. Conditions alternated in an HHSSHHSS pattern that created shift and non-shift response blocks. The participant was then given a target category, and was asked to press the press pad when they saw a word matching this category.

Each word was presented for 300 milliseconds (msec), followed by a 900-msec inter-stimulus interval. The first two word blocks were practice and therefore excluded from the analysis. A 500-msec/450-Hz tone sounded for each false alarm, but not for omissions. False alarms constituted responses to distracter stimuli while omissions were failure to respond to target stimuli. The task took around 10 minutes depending on the level of participant's cognitive impairment.

Outcome measures included:

- *Total commissions or distractor (commission) errors* (e.g., responding to happy words during sad word blocks) during happy and sad word blocks, *during shift and non-shift blocks*
- *Total omissions or target (omission) errors* (e.g., failing to respond to sad words during sad word blocks) during *shift and non-shift blocks*
- *Reaction times or mean correct latency*

Non-Planning Impulsivity

(1) Stockings of Cambridge (SOC)

This task was derived from the Tower of Hanoi (TOH) task and measured non-planning impulsivity (**Shallice, 1982**). A study using Positron Emission Tomography (PET) demonstrated activation in the parietal lobes bilaterally, as well as the left dorsolateral prefrontal cortex (DL-PFPC) and left caudate nucleus in the dorsal striatum (**Baker et al., 1996; Morris et al., 1993; Owen et al., 1996**).

The participant was shown two displays containing three coloured balls (one green, one blue and one red). The displays were presented in such a way that they can easily

be perceived as stacks of coloured balls held in stockings or socks suspended from a beam. This arrangement made the 3-D concepts involved apparent to the participants and fitted with the verbal instructions (**Figure 2.4**).

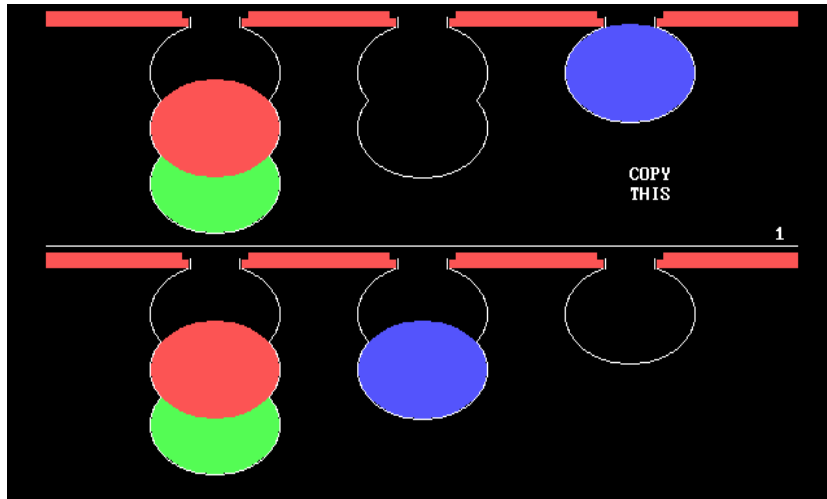


Figure 2.4: CANTAB and Stockings of Cambridge (SOC).

In this task, two sets of three coloured balls were presented, each arranged in three hanging pockets. Participants were asked to move the balls in the arrangement in the lower half of the screen according to specified rules, to match the upper or 'goal' arrangement. The balls were moved one at a time by touching the required ball then touching the position to which it should be moved. The participants were told the minimum number of moves necessary to match the goal configuration and were instructed to use as few moves as possible. This demanded planning and execution of an optimal set of moves that transformed the initial ball configuration to the goal configuration.

Problems could be solved in a certain minimum number of moves (two, three, four or five moves) and participants were instructed to work out the solution prior to moving any balls. The maximum moves allowed corresponded to twice the minimum number possible plus one, or plus two in the case of 'five move' problems. If the maximum number of moves were exceeded the computer indicated 'too many moves' before beginning the next trial. Initial and subsequent 'thinking' latencies during trials were

recorded to provide estimates of cognitive speed during the preparatory and execution phases of task performance.

For each trial, a controlled condition was also executed. During these 'following' trials, participants were instructed to execute a sequence of single moves as quickly as possible. The 'following trials' were exact reproductions of the participant's earlier planning moves. Initial and subsequent movement latencies in these 'following' trials provided estimates of motor speed. These 'movement times' were subtracted from the test condition times, which included both 'thinking times and 'movement times' in order to provide an estimate of cognitive deliberation and planning times in the test conditions.

Therefore the SOC had four outcome measures:

- *Problems solved in minimum moves*
- *Mean moves for 2, 3, 4 and 5-move problems*
- *Mean initial thinking time for 2, 3, 4 and 5-move problems*
- *Subsequent thinking time for 2, 3, 4 and 5 move problems*

(2) Spatial Working Memory (SWM)

Spatial Working Memory (SWM) is a test of the participant's ability to retain spatial information and to manipulate remembered items (**Baddeley & Logie, 1999; Owen et al., 1990; Owen et al., 1995**). It is a self-ordered searching task (**Petrides & Milner, 1982**). Positron Emission Tomography (PET) imaging studies have indicated that this task preferentially activated neural circuitry, which included the dorsal and ventral (DV-PFPC) prefrontal regions (**Mehta et al., 2000; Owen et al., 1996; Robbins et al., 1998**).

The test began with a number of coloured squares (boxes) being shown on the screen. The aim of this test was that, by touching the boxes and using a process of elimination, the participant found one blue 'token' in each of a number of boxes and used them to fill up an empty column on the right hand side of the screen while not

returning to boxes where a blue token had been previously found (**Figure 2.5**). The number of boxes was gradually increased from three to eight boxes. The number of tokens always equaled the number of boxes. The colour and position of the boxes used were changed from trial to trial which discouraged the use of stereotyped search strategies. The task took around 8 minutes, depending on level of impairment.

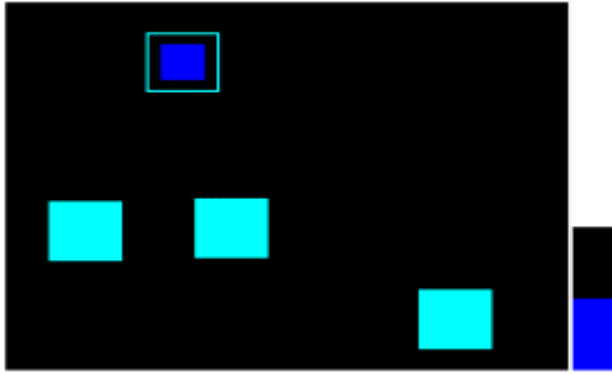


Figure 2.5: CANTAB and SWM. Figure illustrating one blue ‘token’ in one of the four boxes with two other blue tokens already found and placed in the column on the right hand side of the screen.

Consequently, four types of search errors were possible:

- (1) *Between-search error (BSE)*: When participants returned to a box where a token had already been found.
- (2) *Within-search error (WSE)*: When participants returned to a box that was already opened and shown to be empty earlier in the same search sequence.
- (3) *Double-search errors (DSE)*: Occasions where the participant had committed an error that could be categorised as both a within and a between error.
- (4) *Total search errors (TSE)*: The number of times a box selected that is certain not to contain a blue token and therefore should not have been visited by the participant (i.e. between errors+ within errors – double errors).

A *strategy score* was also derived from this task. A common strategy employed in the performance of this task was to follow a predetermined sequence, beginning with one box and returning to start each new search with that box after a token has been found (repetitive search strategy). Such strategies, when applied to self ordered search tasks of this type, served to reduce the load on active working memory and would, presumably, enhance performance at all levels of task difficulty. The strategy

score was calculated by counting the number of different boxes initially opened at each trial, hence, the lower the strategy score, the more efficient was the participant.

Other SWM outcome measures include:

- *Mean time to first and last response*
- *Mean token search preparation time*

(3) Spatial Span (SSP)

Spatial Span Task is a visuo-spatial analogue of the Digit Span Test and a computerized version of the Corsi Blocks Tapping Task (**Milner, 1971**). This task assessed the participant's ability to remember the spatial locations of a sequence of white boxes on a computer screen and was believed to preferentially activate neural circuitry that included the right ventrolateral prefrontal cortex and the parietal cortex (**Owen et al., 1990; Robbins et al., 1994**). It is predominantly a measure of short term memory but also involved in the executive component of working memory (**Baddeley, 2003**).

On each individual trial, an array of nine white boxes was displayed on the screen. Participants watched while each white box changed colour before being asked to reproduce this sequence. The length of the sequence presented began with two boxes and increased steadily up to a maximum of nine (**Figure 2.6**).

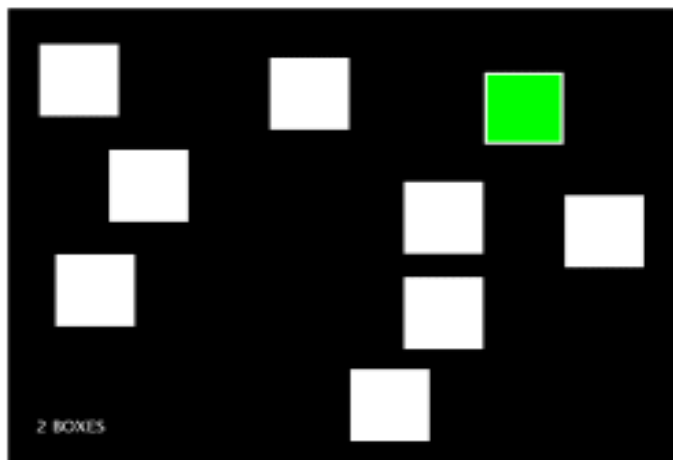


Figure 2.6: CANTAB and SSP. Participants watching while 2 of the 9 white boxes changed colour before being asking him/her to reproduce this sequence.

A participant's spatial span was defined as the longest sequence that they can reproduce correctly within three attempts.

Therefore outcome measures for this task included:

- *Span length*
- *Total usage errors*
- *Mean time to first and last response (latency)*
- *Number of attempts*

Cognitive Flexibility

Intra/Extra-Dimensional Set Shift (IED)

Intra/Extra-Dimensional Set Shift (IED) is a test of rule acquisition and reversal. This task, previously described by **Downes *et al.* (1989)**, examines the ability to attend to specific attributes which include visual discrimination, attentional set formation maintenance, shifting and flexibility of attention (**Robbins & Roberts, 2007**). This test is a computerised analogue of the Wisconsin Card Sorting Test (WCST) and is sensitive to changes to the DL-PFC and VL-PFC areas of the brain (**Elliott *et al.*, 1995; Downes *et al.*, 1989; Durstewitz *et al.*, 2000**). The IED took seven minutes to complete depending on the level of cognitive impairment.

This task assessed a participant's ability to first focus attention on specific attributes of compound stimuli (intra-dimensional stages) and then to shift attention, when required, to a previously irrelevant stimulus dimension (extra-dimensional stages). Here 'dimension' refers to the attributes of an object such as different shapes and colours. In this study the two artificial dimensions used were colour-filled shapes and white lines. Simple stimuli were made up of just one of these dimensions, whereas compound stimuli were made up of both, namely white lines overlying colour-filled shapes. The participant started by seeing two simple colour-filled shapes, and must learn which one was correct by touching it (**Figure 2.7**).

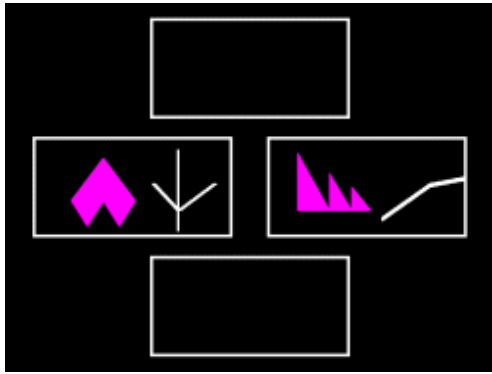


Figure 2.7: CANTAB and IED Task. Participant asked to choose between two artificial dimensions (compound stimuli).

Feedback helped the participant to understand which stimulus was correct, and after six correct responses, the stimuli and/or rules were changed. At this point distracting stimuli (lines) were added in order to provide compound discrimination stages (CD1 and CD2). These shifts were initially intra-dimensional (e.g. colour filled shapes remained the only relevant dimension). After this stage has been learnt, there was an Intra-Dimensional Shift (IDS), where new exemplars of the two dimensions 'line' and 'shape' were introduced, but the relevant dimension was unchanged (e.g. colour-filled shapes remained the only relevant dimension). After an Intra-Dimensional Reversal (IDR), there followed an Extra-Dimensional Shift (EDS), when for example white lines became the relevant dimension followed by a final reversal stage (EDR) (Figure 2.8).

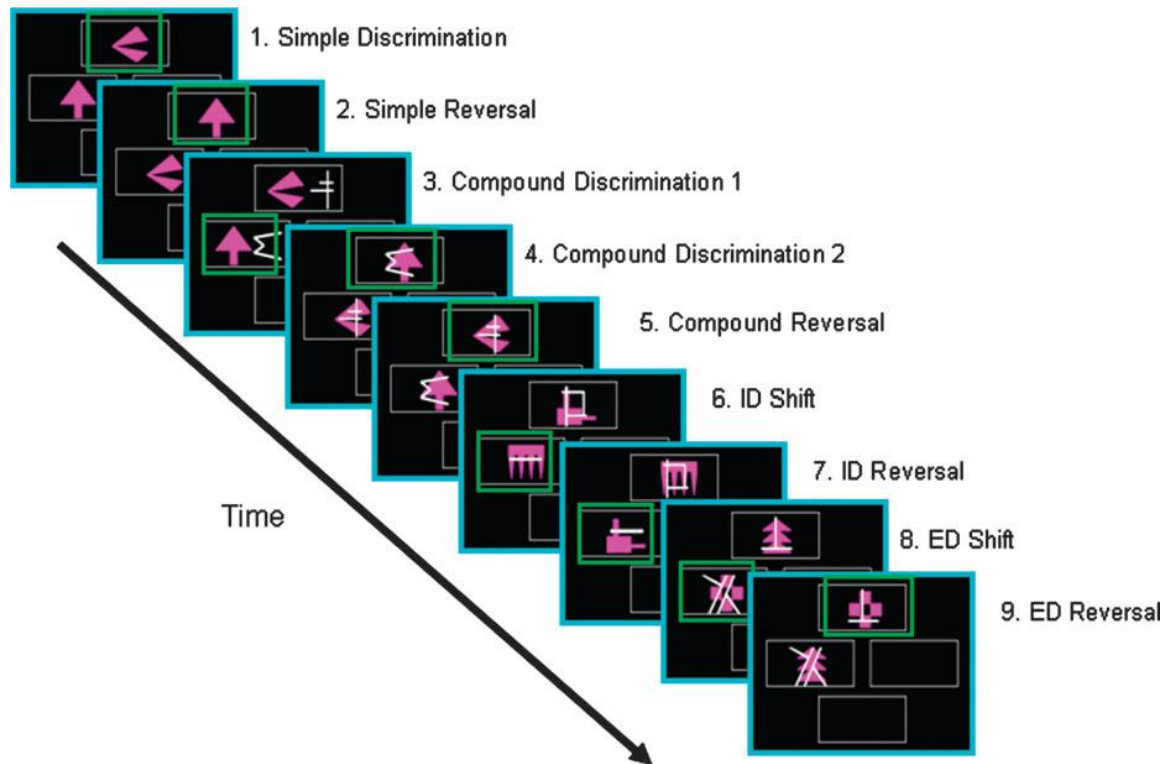


Figure 2.8: Schematic of the IED Task. The correct choice for each stage was marked with a green box.

Therefore the task proceeded through a series of stages, each with a different contingency (up to a maximum of 9 stages) (**Figure 2.8**):

- (1) *Simple Discrimination (SD)*: between two pink shapes or white lines.
- (2) *Simple Reversal (SDR)*: using the same stimuli but with the contingencies reversed.
- (3) *Compound Discrimination (C_D or CD1)*: the contingencies were the same, but now there was the addition of a new pattern of either lines or shapes ('distracters') which were kept separate and the two patterns on the screen do not overlap. The pairings of the lines and shapes was pseudo random, with no more than three consecutive trials with the same pairings.
- (4) *Compound discrimination (CD or CD2)*: with stimuli overlapping, with contingencies kept the same, except for the overlap of the two patterns.
- (5) *Compound Reversal (CDR)*: the contingencies were reversed but the correct response was within the same dimension.

During the above stages 1–5 (known as the discrimination and learning phases) participants could learn through trial and error to select one specific shape while ignoring the other shape and lines. The computer gave the participant feedback ('correct' in the colour green or 'wrong' in the colour red). The participants could learn a rule to follow to assure that one continued to make correct choices. The type of shapes or lines presented in stages 1–5 remained the same.

(6) *Intra-Dimensional Shift (IDS)*: This is the intra-dimensional shift stage, wherein a new set of exemplars was presented and success depended upon continuing to sort according to lines or shapes.

(7) *Intra-Dimensional Reversal (IDR)*: the contingencies within the same stimulus dimension were now reversed.

(8) *Extra-Dimensional Shift (EDS)*: The previously ignored dimension, the 'distractor', was now the correct dimension by which to sort. That is, if shapes were previously correct, now the subject needed to sort according to the lines that were reinforced randomly. Stage 8 is analogous to a change in category in the Wisconsin Card Sorting Test and requires conceptual flexibility (**Owen *et al.*, 1991; Rogers *et al.*, 2000**). Set-shifting represents the ability to switch attention from one aspect of a stimulus to another in an ongoing task, as a result of changing reinforcement contingencies (**Birrell & Brown, 2000**).

At this point, the participant was expected to incur an additional challenge because they were required to make a substantial shift away from the dimension that had been salient for the previous seven tasks, which required only perceptual flexibility (**Luciana & Nelson, 1998**).

(9) *Extra-Dimensional Reversal (EDR)*: Here, the contingencies were reversed within the new stimulus dimension.

The task involved nine stages with participants proceeding to the next stage when they attain a criterion of six consecutive correct responses. Failure to achieve this criterion within 50 trials resulted in the premature discontinuation of the test.

The main outcome measures of the IED included:

- *Numbers of trials and stages successfully completed*
- *Errors* (i.e. instances when participant failed to select the stimulus that was compatible with the current rule) at each stage, up to the extradimensional shift (*pre-EDS errors*) and at the extradimensional shift (*EDS errors*).
- *Attrition rate* (inability to complete the test resulting in termination of the actual tests). Since this has not occurred to any of the four study groups data from this part of the task were not analysed in any detail and were not discussed further.

Memory and Learning

(1) Delayed Matching to Sample (DMS)

Delayed Matching to Sample (DMS) Task assessed forced choice recognition memory for novel non-verbalisable (visual) complex and abstract patterns by testing both visual matching ability and delayed visual recognition memory. The problem of control of a stimulus that has disappeared has long been studied in experimental psychology (**Hunter, 1913**). The delayed matching-to-sample procedure was used in a classical experiment by **Blough (1959)** and has often been used to study 'remembering' in non-human animals (**Sargisson & White, 2001; Urcuioli & Zentall, 1986**). Lesion studies suggest that this task was sensitive to temporal lobe or amygdale-hippocampal damage (**Owen *et al.*, 1995**).

At the beginning of each trial, a complex, visual and multicoloured pattern consisting of four quadrants (stimulus) appeared in the centre of the screen in a box for a presentation period of 4.5 seconds (**Figure 2.9**).

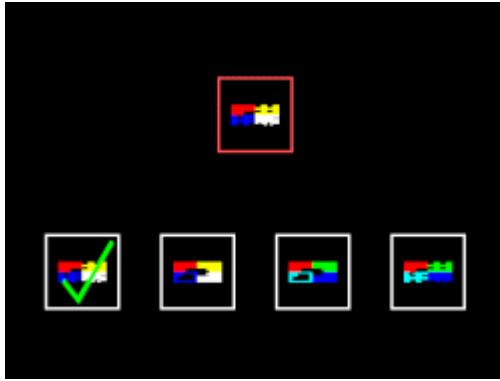


Figure 2.9: CANTAB and DMS showing simultaneous matching.

After presentation of the stimulus, the participant choose the identical pattern from a set of four stimuli (one correct and three ‘distractors’) after variable periods of 0 or immediately, 4 and 12 second delay (also known as *delayed matching*) or during a *simultaneous matching* condition in which the target and four choices appeared together (**Figure 2.9**).

Only one of the choice patterns is identical to the target. One of the other choice patterns is a novel distracter, differing in both colour and form from the target. The remaining two choice patterns are ‘partial distracters’ in that one has the colours of the target but the form of the novel ‘distracter’, whilst the other has the form of the target but the colours of the novel ‘distracter’. In addition, each of the four choice patterns has one (random) quadrant in common to discourage mnemonic strategies based on remembering the colour and form of a single quadrant.

The participant’s response elicits an auditory tone and visual feedback in the form of green ticks and red crosses. If the participant made an incorrect response they were required to continue to choose until the target stimulus was chosen.

Following one practice trial (simultaneous, 0 second and 12 second delays), a total of four sets of 10 trials were presented with each of the four conditions presented in a pseudorandom order. The task took about 15 minutes to complete all trails.

The primary outcome measures in this task included:

- *Speed of response*
- *Total number of correct targets chosen at each of the simultaneous and delay conditions.* The difference between simultaneous and delay conditions gave a good overall impression of visual memory ability.

(2) Paired Associate Learning (PAL)

Paired Associate Learning (PAL) Task assesses visual working memory and visuo-spatial associative learning (explicit memory). The task contains aspects of both a delayed response and conditional learning procedures. The explicit memory component of this task is considered as part of fronto-temporal function (**Potvin et al., 2005**).

In the initial (presentation) stage the six boxes were displayed on the screen and opened in a pseudo-random order, one at a time for three seconds to reveal a different pattern (complex stimuli) inside. One or more of these boxes contained a pattern. After a brief delay the patterns were then displayed in the middle of the screen (recall stage), one at a time. The participant was then asked to touch the box where the pattern was originally located. If the participant made an error, the patterns were re-presented to remind the participant of his/her locations so that the participant had another opportunity to indicate the correct locations (**Figure 2.10**).

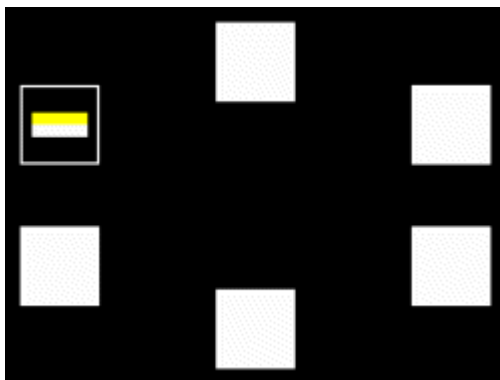


Figure 2.10: CANTAB and PAL. The participant was asked to touch the box and successfully identify where the pattern was originally located.

The test began at a very easy level with a single pattern in one of the boxes. Then gradually the test became more difficult with two and three pattern sets before tests with six and finally eight items (eight boxes on the screen) were finally reached. This ensured that the tests were suitable for varying level of neuropsychological impairment. Feedback was not provided after each participant response, but if all choices were correct the words 'all correct' appeared on the screen and the computer progressed to the next sequence. If the choice were incorrect, the boxes reopened for a further two seconds each, and the participant was given further attempts (up to a maximum of 10 trials in total, at which point the programme terminated) until he/she choose all correct locations. The task took about 10 minutes to complete all trials.

The main outcome measures in this task included:

- *Total number errors made*
- *Number of trials required to locate the pattern(s) correctly*
- *Stages completed*
- *Memory scores.*

(3) Pattern Recognition Memory (PRM)

The Pattern Recognition Memory (PRM) Test is a two-choice forced discrimination paradigm and assesses the participant's ability to recognise a previously presented abstract pattern from two adjacent stimuli. This test was often used, in conjunction with Spatial Recognition Memory (SRM) , before the Paired Associates Learning (PAL) task as both these tests helped to train the subject for PAL. PRM and SRM contained different elements of PAL and the results considered together help to decide on the exact nature of the neuropsychological deficit being considered (**Sahakian *et al.*, 1988**). Lesion studies suggested that this task was sensitive to either temporal lobe or amygdale-hippocampal, but not to frontal lobe excision (**Owen *et al.*, 1995**).

This task was presented in two phases. Initially the participant was presented with a series of twelve simple but abstract, coloured visual patterns, appearing one at a

time, inside a white box located in the centre of the screen (presentation phase). These patterns were designed so that they cannot easily be given verbal labels and no encouragement was given to the participant to use verbal labels. Each of these 'target' patterns was presented for 3 seconds, the screen was then cleared and the next pattern appeared.

Following a 5 second delay in the second recognition phase, the participant choose between a pattern he/she has already seen or a novel (distracter) pattern that differed in form but not in colour from the target (**Figure 2.11**). The participant then made a 'forced-choice' discrimination by touching the pattern he/she has seen previously. In this phase, the test patterns were presented in the reverse order to the original order of presentation. The participant was then required to respond to each pair by touching the pattern they had already seen during the presentation phase. Each response was accompanied by an auditory tone and visual feedback was automatically provided by the computer in the form of green ticks (for correct responses) and red crosses (for incorrect responses).

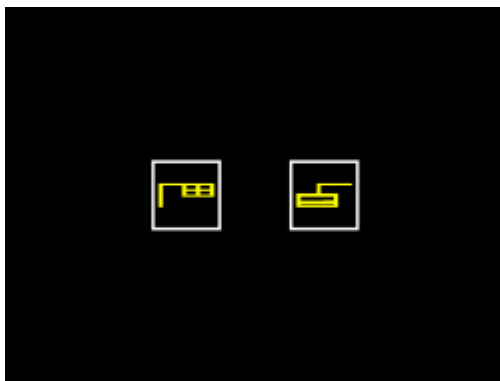


Figure 2.11: CANTAB and PRM during the recognition stage.

This procedure was then repeated with 12 new patterns in each set. The task took about 5 minutes to complete all trials. The primary outcome measures in this task included:

- *Mean response latency*
- *Number of correct locations chosen across the two trials*

(4) Spatial Recognition Memory (SRM)

The Spatial Recognition Memory (SRM) Test is a two-choice forced discrimination paradigm and assessed the participant's ability to recognise and remember the spatial locations of target stimuli. This test was often used, in conjunction with Pattern Recognition Memory (PRM) , before the Paired Associates Learning (PAL) task as both these tests helped to train the subject for PAL. A study using PET scanning has shown that this task activates the dorso-lateral prefrontal cortex (**Goldberg *et al.* 1996**), and lesion studies suggested that it was sensitive to frontal but not temporal or amygdale-hippocampal lesions (**Owen *et al.* 1995**).

The participant was presented with a series of five (one-inch) white squares, appearing, one at a time, in sequence at five different locations on the screen (presentation phase). Each square was presented for three seconds before the screen was cleared and the next square appeared. The participant was instructed to remember the location of the five boxes presented.

In the recognition or discrimination phase, the participant saw a series of five pairs of squares, one of which was in a place previously seen in the presentation phase (target location) (**Figure 2.12**). The other square (distracter square) was in a location not seen in the presentation phase (novel location). The participant was then asked to select which of the two locations had been shown earlier.

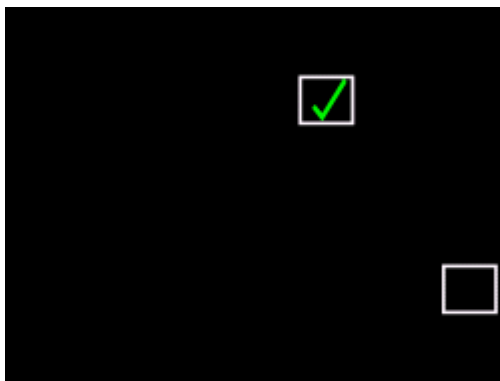


Figure 2.12: CANTAB and SRM with correctly identified target location paired with a novel location.

Locations were tested in the reverse of the presentation order. This sub-test was repeated four more times, each time with five new locations giving a maximum possible score of 20. Again, each response was accompanied by an auditory tone and visual feedback in the form of green ticks for correct responses and red crosses for incorrect responses. The task took about 5 minutes to complete all trials.

The primary outcome measures in this task included:

- *Mean response latency*
- *Number of correct locations chosen across the four trials*

Table 2.4: Summary of neuropsychological tasks used in the study and their key outcome measures.

Test	Measure
National Adult Reading Test (NART) v2.0.	WAIS-R Full Scale (IQ=70-131), Verbal Scale (IQ=72-127) and Performance Scale (IQ=74-128).
CANTABeclipse v3.0.	
Motor Screening and Big Little Circle (BLC).	Not measured.
Cambridge Gambling Task (CGT).	Quality of Decision Making. Risk Taking and Overall Proportion Bet Deliberation Time or Latency. Delay Aversion and Risk Adjustment.
Affective Go-NoGo (AGN).	Total Commissions/Distractor Errors. Total Omissions/Target Errors. Correct Mean Latency or Reaction Times.
Stockings of Cambridge (SOC).	Initial Thinking Times (at each stage). Subsequent Thinking Times (at each stage). Problems solved in minimum number of moves.
Spatial Working Memory (SWM).	Total Search Errors (mean, 4, 6, 8 move problems). Between, Within and Double Search Errors (mean, 4, 6, 8 move problems). Strategy Score. Mean Time to First and Last Response. Mean Token Search Preparation Time.
Spatial Span (SST).	Span Length and Total Errors. Total Usage Errors and Total Number of Attempts. Mean Time to First and Last Response.
Intra/Extra-Dimensional Set Shifting (IED).	Number of Trials and Stages Completed. Total Number of Errors. Pre-EDs Errors and IDS Errors
Delayed Matching to Sample (DMS).	Mean Correct Latency or speed of response. Total Correct Responses(0,4,12 & simultaneous).
Paired Associate Learning (PAL).	Mean Total Number of Errors and Trails. Stages Completed and on 1 st Trial. Memory Score.
Pattern Recognition Memory (PRM).	Mean Correct Latency and Total Number of Trials.
Spatial Recognition Memory (SRM).	Mean Correct Latency and Total number of Trials.

Parallel batteries

The CANTAB tests presented in this thesis referred to the standard tests selected from the batteries used at baseline testing (i.e. the clinical version). Parallel versions of the tests were used when the same participant was tested more than once. Parallel versions for Delayed Matching to Sample (DMS), Intra-Extra/Dimensional Set Shifting Task (IED), Paired Associate Learning (PAL), Pattern Recognition Memory (PRM), Spatial Recognition Memory (SRM), were available and used.

The parallel versions differ in three key aspects:

- (1) The parallel batteries presented the participant with different patterns and locations to be remembered. Specifically, the tasks involved different patterns in each battery. (Pattern Recognition, Delayed Matching to Sample, Paired Associate Learning). The Spatial Recognition Memory task varied the locations of the boxes to be remembered.
- (2) Some of these tests (e.g. Paired Associate Learning) were shorter in duration due to a reduction in practice trials.
- (3) The Big/Little Circle, Stockings of Cambridge, Cambridge Gambling, Spatial Span and Affective Go-NoGo tasks were not presented within parallel versions and so participants performed these tasks using the clinical version during repeated testing.

Statistical analysis

General considerations

This study tested several hypotheses using potentially a large number of outcome variables. When a significant difference in scale was recorded between groups one needed to be careful that the difference was also meaningful. Difference was measured in adjusted *p*-values (and effect size if significance reached). All data analysed were either continuously distributed measurements or dichotomised responses. All analyses were conducted using SPSS for Windows V.12 (SPSS Inc. Chicago Ill.).

Power calculations

The power calculation for the numbers of participants required to reliably detect differences between the HEROIN and METHADONE groups in this study was hampered by the lack of comparable data.

The power calculations were therefore based on the data reported by **Ornstein *et al.* (2000)** and **Rogers *et al.* (1999a)**. To detect a difference of three on the strategy score for the Spatial Working Memory Task (estimated to represent a conservative measure of a 'real-world' functional impairment in executive functioning) and to obtain a power of 0.8 (with $\alpha=0.01$, two-tailed) the study required 17 completing participants in the HEALTHY CONTROL and in the three experimental groups. To detect a difference of 1 in the number of perseverative responses made during the simple discrimination reversal stage of the IED task and to obtain a power of 0.9 (with $\alpha=0.01$) the study required 15 completing participants. To accommodate a likely attrition rate of 40%, we attempted to recruit 28 participants in each of the four groups.

Homogeneity of distribution and standard deviation

Initial descriptive analyses were conducted to determine whether data met normal distribution.

This was tested by:

- (1) Visually displayed a normal curve on a histogram and determine its 'fit' with the sample data.
- (2) *Quantile-Quantile (Q-Q) or Probability-Probability (P-P) Plots* using z-scores (**Field, 2009**). If the data was normally distributed the observed data 'fit' exactly along the straight line of the plots.
- (3) Evaluating the *skewness* ('asymmetry' of distribution) and *kurtosis* ('pointedness' of the shape of the distribution) of the data analysed. So a normal distribution would have a *skewness* of 0 and a *kurtosis* of 0. A departure from symmetry was taken to

exist if absolute value of *skewness* and/or *kurtosis* was more than 1.96 times the Standard Error (SE).

(4) *Kologorov-Smirnov (K-S) Test* (Field, 2009). A significant value of $p < 0.05$ indicated deviation from normality.

Although the assumption of normality of distribution was made in the derivation of many significance tests, its importance in the analysis of a data set remains controversial (Tabachnich & Fidell, 1996). For example, sample size effects the degree to which deviation from normality (non-normality) may affect robustness – the larger the sample size the smaller the effect non-normality is likely to have on both power and significance level (Pearson, 1929). The relatively small sample size in the present study was likely to have increased the effects of non-normality on robustness. The majority of theorists in this field argue that violation of the normality assumption should be of little concern for most parametric tests (Pearson, 1931; Rider, 1929; Tabachnich & Fidell, 1996). Games & Lucas (1966) reported that the effect of non-normality on power of Analysis of Variance (ANOVA) was only significant when the non-normal populations were extremely skewed or leptokurtic. Moderate departures from normality had minimal impact on the power or sensitivity of tests. However, the literature on robustness of significance testing and the degree to which assumptions can be violated is far from conclusive.

The CGT, AGN, SRM, SWM, DMS and SSP tests met assumptions of normality and homogeneity of variance were analysed using ANOVA as a *between subject factor*.

Homogeneity of variance

Levene's Test (F) tested the null hypothesis that the variances in the four independent groups studied were equal. If Levene's Test was significant at $p < 0.05$ then we concluded that the null hypothesis was incorrect and that there was heterogeneity of variance.

The robustness of ANOVA to violation of homogeneity of variance has been intensively studied. Guidelines (**Glass *et al.*, 1972**) have become more stringent than the earlier, more cavalier ones (**Box, 1953**). The effects of violating both normality and homogeneity of variance assumptions were regarded as compounding the impact on power and significance of the *F*-test.

Dealing with non-normality and unequal variances: transformation of data

For some non-normal distributions a transformation can be found, which brings the data more closely in line with the normal distribution (**Tabachnick & Fidell, 1996**). This depended on the relationship between the variances and the group means (**Tukey, 1977**). Where necessary, to stabilise variance and to diminish skewness and kurtosis, data were subjected to either square root (*SQRT*) or logarithmic transformation (*log10*) (**Fields, 2009**). Parametric statistics using ANOVA were subsequently conducted. The IED, PRM and SOC outcomes were *SQRT* transformed and PAL outcomes were subjected to *log10* transformation.

When transformation was either not possible or the data failed to meet the homogeneity of variance assumption, analyses were conducted using non-parametric statistics using Kruskal-Wallis one-way analysis of variance. No outcomes were analysed using non-parametric test. In addition non-parametric tests were also used in order to determine whether results from the analysis with transformed data could be replicated (**Rasmussen & Dunlap, 1991**).

Levels of difficulty in neuropsychological tests: repeated measures analysis

In cases where the tasks included incremental levels of difficulty within the testing session it was not possible to use simple ANOVA due to the need to include a second *within-subject* variable *difficulty* levels, e.g. Cambridge Gambling Task (ratio of coloured boxes), Stockings of Cambridge (2, 3, 4 or 5 problem moves), Spatial Working Memory (between/within search errors), Spatial Span (span length between 1-9), Delayed Matching to Sample (0, 4 and 12 second delays), and Paired Associate Learning (1,2,3,6, or 8 shapes). In the CGT one also conducted another *within-subject*

variable *direction* (descending and ascending orders) level analysis. In all these situations, a repeated-measures ANOVA was conducted.

The homogeneity of variance across groups in repeated-measures design ANOVAs was assessed by the Mauchly Sphericity Test (**Mauchly, 1940**). Where data sets significantly ($p < 0.05$) violated this requirement for a repeated-measures design ANOVA, the Greenhouse Geisser Epsilon ($\hat{\epsilon}$) correction parameter for degrees of freedom (**Greenhouse & Geisser 1959; Winer *et al.*, 1991**) was used to calculate a more conservative p value for each F ratio.

Comparison (*a priori* and *post hoc* contrasts) of data

The F -ratio informs only whether the model fitted to the data accounted for more variation than extraneous factors, but it does not inform where the differences between groups lie. It was therefore necessary after conducting an ANOVA to carry out further analysis to find out which out of the four experimental independent groups differed (or not). This has been done using both a planned (*a priori*) and a *post hoc* (**Field, 2009**) comparison or contrast. *A priori* comparisons implied that the difference might exist but to be completely sure *a post-hoc* tests were always conducted throughout the analysis.

Figure 2.13 illustrates the planned contrasts used based upon the hypothesis being tested.

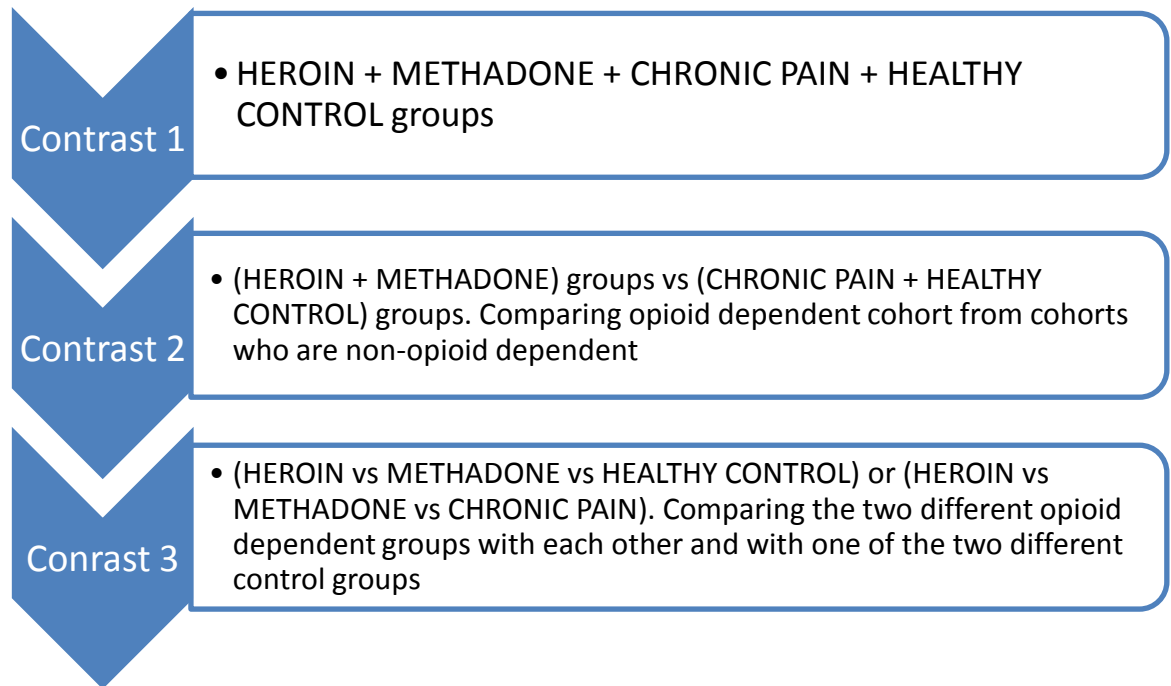


Figure 2.13: Planned Comparisons/Contrasts (*a priori*) based upon the hypotheses being tested in this study.

Post-hoc tests consisted of pairwise comparisons, which controlled for family wise error by correcting the level of significance, such that the overall Type 1 error rate (α) across all comparisons remained at 0.05. The trade off to this procedure is that it created a loss in Type 2 (β) error due to loss of statistical power. In this study conservative tests were used to control Type 1 error due to the small number in experimental groups and large number of neuropsychological variables present. The *post hoc* test used in this study was the *Bonferroni* correction (Fields, 2007).

Multiple testing

Since the number of families of neuropsychological tests in this study was five, as described in Chapters 1 and 2, the 5% significance level needed to be adjusted. The significance level was divided by the number of tests so that only statistical significance with $p < 0.01$ will be considered (Sainani, 2009; Ioannidis, 2005). This minimised effects due to multiple comparisons, subgroup analyses and/or repeated measures when one was considering a family of statistical inferences simultaneously.

Even though all multiple comparisons were *post hoc Bonferroni* corrected, this process helped in applying caution in the interpretation of the results obtained in this study (**Sainani, 2009**).

Significance levels

If a test gives a p -value lower than the significance level α , the null hypothesis is rejected. Smaller levels of α increases confidence in the determination of significance, but run an increased risk of failing to reject a false null hypothesis (Type II error) and so have less statistical power. The selection of the level α thus inevitably involves a compromise between significance and power, and consequently between the Type I error and the Type II error. More powerful studies can obviate this choice to an arbitrary degree (**Fields, 2007**).

Results below a p level of 0.01 were described in this thesis as significant. They were then qualified as achieving $p < 0.01$, $p < 0.005$ or $p < 0.001$ levels accordingly. Outcome data between $p < 0.05$ and $p > 0.01$ were described in this thesis as having a non-significant trend if they were considered relevant to substantiate the interpretation of the significant results.

Effect size calculations

Effect sizes were calculated when appropriate and when results were significant. An effect size is a measure of the magnitude or strength of a relationship between two variables or the degree to which the null hypothesis is false (**Borenstein et al., 2009**).

The calculation of effect sizes standardised the magnitude of the difference between groups such that a 1-point difference indicated that the groups differed by 1 standard deviation on a particular outcome measure. There were several different techniques for calculating effect sizes. In this study Cohen's d which was defined as the difference between two means divided by the pooled standard deviation for those means was used (**Cohen, 1992**).

Cohen's d was calculated using the formula:

$$d = \frac{(\text{mean1} - \text{mean2})}{\sqrt{(SD1^2 + SD2^2) / 2}}$$

SD = Standard Deviation.

Cohen suggested that an effect size (d) of ≤ 0.2 should be considered small, 0.5 – 0.79 medium and more than 0.8 as large (Cohen, 1992).

Specific statistical considerations relevant to the neuropsychological assessments

The Cambridge Gambling Task (CGT) had six outcome measures, each of which had one or two options applied to it. The options were categorised into gamble type (ascending or descending orders) expressed as *direction* and ratio (5:5; 4:6; 3:7; 2:8; 1:9) chosen expressed as *difficulty*. Therefore analysis on quality of decision making, deliberation time, risk taking and risk adjustment were conducted together for *direction* and *difficulty* and then separately (Passetti *et al.*, 2008; Fishbein *et al.*, 2007; Ersche *et al.*, 2005a, 2005b).

For analysis of performance on the Affective Go-NoGo (AGN) task, trials were divided into two options. Option 1 was shift or non- shift and Option 2 tested the negative or positive valence target types. Therefore analysis on commissions, omissions, and latency data were conducted separately for option 1 and 2.

In the Stockings of Cambridge (SOC) task comprised mean moves during a 2, 3, 4 and 5-move problems (*difficulty* levels), and mean initial and subsequent thinking times. Therefore analyses of data were conducted separately for all above four move problem scenario. This method of analyses was used in other studies using this task (Ornstein *et al.*, 2000; Fishbein *et al.*, 2007a; Ersche *et al.*, 2005a, 2005b).

The Spatial Working Memory (SWM) task comprised of between, within, double and total errors during a 4, 6, 8-box problems (*difficulty* levels). Analyses of data were conducted separately for all above three move problem scenario.

The Intra/Extra-Dimensional (IED) Set Shifting task had been analysed in studies using the CANTAB tests in a variety of ways (**Ersche *et al.*, 2006b**). Measures analysed in this study were the total number of stages the participant completed successfully, total number of trials completed on all attempted stages and errors at every stage. This included analysis of data reaching ID Shift and Reversal (Stages 6 & 7 or also known as Pre-EDS stage), ED Shift and ED Reversal stages (Stages 8 and 9). Analysis was conducted in accordance with other studies using this task in opioid dependent individuals (**Ornstein *et al.*, 2000**).

The Delayed Matching to Sample (DMS) task composed of a simultaneous condition and three delay (0, 4, & 12 second) conditions. Unlike the simultaneous condition, where the target stimulus remained on the screen, the delay conditions assessed the participant's ability to recognise the target pattern from memory. Therefore analyses on percentage correct and latency data were conducted separately for simultaneous and delay conditions. This method of analyses was used in other studies using this task (**Owen *et al.*, 1995**).

For the Pattern and Spatial Recognition Memory (PRM & SRM) tasks data from outcomes measuring number of trials and latency were analysed as a total of all the blocks tested.

Specific statistical considerations relevant to the hypothesis driven analysis

Specific statistical considerations relevant to the analyses presented were described at the beginning of Chapters 4, 5 & 6.

Ethical and research governance

Dr Alex Baldacchino was the registered Chief Investigator for this study with Professor Keith Matthews and Professor David Balfour as co-investigators.

The study was approved by the Tayside Committee on Medical Research Ethics (A) administered by the East of Scotland Research Ethics Service. The REC reference

number is 06/S1401/32 and the study was approved on the 5th May 2006. The study also had favourable ethical approval from the University of St Andrews Ethics Committee on the 9th January 2008.

Site Specific Assessment (SSA) approvals were given to all study sites (SSA reference numbers: 06/S0501/33; 34; & 35) and subsequently NHS Fife and NHS Tayside Management Approvals were issued.

The University of Dundee accepted to be the sponsor to this study under the Research Governance Framework (RGF) for Health and Community Care (Ref: EB/LM/LET201/18184).

The study was also registered on the NHS Fife Information Services Database Register in order to comply with the Data Protection Act 1998. The study was then audited by NHS Fife Research and Development Department on the 11th November 2008 and the 17th November 2010 on both occasions giving a favourable opinion.

Chapter 3: Results-Descriptive Data

The aims of this study were to determine if:

1. Chronic exposure to opioids (prescribed and/or illicit) is associated with measurable neuropsychological deficits. Specifically it was predicted that these deficits were greatest on measures of so-called 'executive neuropsychological functioning'- the abilities to plan, to organise and to sequence behaviour.
2. The deficits identified depend upon the *nature* of the opioid (long acting opioids compared with short acting opioids) or the *context* (prescribed opioids compared with illicit opioids) or *status* (opioid dependence compared to non – opioid dependence and injecting compared to non-injecting opioid dependent) in which it was used.

The hypotheses to be tested are:

1. Is chronic opioid dependence associated with neuropsychological impairment reflected in altered performance on measures of impulsivity, cognitive flexibility and memory?
2. In patients with chronic opioid dependence, is injection status associated with neuropsychological impairment as reflected in altered performance on measures of impulsivity, cognitive flexibility and memory?
3. In patients with chronic opioid dependent is the degree of acute opioid exposure (acute intoxication, withdrawal or stable initial exposure to methadone), or duration of opioid exposure (period of methadone maintenance) associated with neuropsychological impairment as reflected in altered performance on measures of impulsivity, cognitive flexibility and memory?

Statistical considerations

Basic statistical considerations have been described in Chapter 2 of this thesis.

Baseline demographic characteristics of cohorts and control populations

Full details of the recruitment and assessment process were described in Chapter 2 of this thesis .To summarise:

1. **HEROIN Group:** Twenty four male participants were recruited aged between 18 and 30 years old entering a structured methadone maintenance treatment programme and attending Tayside and Fife NHS Addiction Services. The participants had confirmed histories of more than three years of regular, daily illicit opioid (heroin) use and met criteria for a diagnosis of opioid dependence syndrome according to DSM-IV. To merit inclusion, they were required to be taking between 0.4 g and 1.5g of heroin intravenously daily, or to have smoked heroin such that they have achieved a similar degree of drug exposure leading to an estimated equivalent daily methadone dose of 40-120mg. They were naïve to methadone and other types of prescribed opioids. These participants were assessed on entry to, and following stabilisation with, methadone within the treatment programme.
2. **METHADONE group:** Twenty nine opioid dependent males aged between 18 and 30 years old were recruited. They have been stable on methadone for more than six months with retrospective objective confirmation of the absence of illicit drug use (including heroin) during this period. Eighteen of these participants were followed up after a further six months and re-evaluated to identify changes in cognitive functioning.
3. **CHRONIC PAIN Group:** Twenty eight males were recruited from the NHS Tayside Chronic Pain Clinic, aged between 18 and 40 years, who had a history of more than three years of continuous prescribed opioids, with no past or current history of illicit drug (e.g. heroin) use and/or methadone treatment.

4. **HEALTHY CONTROL group:** Twenty eight healthy control males aged between 18 and 40 years old were recruited. They had no past or current history of chronic pain and/or illicit substance use, or a lifetime continuous/regular prescription of opioids.

The cohort of non-heroin abusing individuals (CHRONIC PAIN) recruited from the Chronic Pain Clinic, helped identify the possible effects of drug adulterants and other potential confounders present in a 'drug addict lifestyle'. The cohort of methadone maintained and stable individuals (METHADONE) helped to retrospectively identify the possible contamination effect of previous illicit heroin use in the HEROIN group and prospectively test for deterioration or improvement.

Representativeness of the recruited opioid dependent groups (HEROIN and METHADONE groups)

The demographic characteristics of the recruited cohort who completed the study testing were compared with those of (a) the total opioid dependent population on a national and regional level, (b) the local drug-treatment seeking population who did not want to participate (non-participants) and (c) participants who did not complete the study (non-completers).

For estimates of problem drug use in the United Kingdom information was collected from those in contact with general practitioners, outpatients or community based drug services and inpatient services using either capture-recapture or multiple indicator methodologies (**Frischer *et al*, 2004; EMCDDA, 2008**). This provided the opportunity to compare the demographic characteristics of the UK drug taking population with that of the characteristics of the HEROIN and METHADONE groups in this study.

Other sources of comparison included information obtained from the (a) National Treatment Outcome Research Study (NTORS) (**Gossop *et al*, 1997**), (b) National Drug

Treatment Monitoring System (NDTMS) (Hay & Bauld, 2008) and related Drug Treatment Outcome Research Study (DTORS) (Jones *et al.*, 2007) for England and the (c) Drug Misuse Prevalence Study (Hay *et al.*, 2005) through the Information Services Division (ISD) for Scotland. All these databases were based on systematic recording of national datasets on patients seen at a broad range of services and held information on demographic and behavioural characteristics of patients attending treatment services.

Table 3.1: Comparison of the sociodemographic characteristics of study participants with histories of opioid dependence (HEROIN and METHADONE groups) and those reported in earlier population studies and estimates provided by ISD.

	N	Mean age (yrs)	Male (%)	SIMD	Ethnicity % white	Unemp (%)	Stable housing Status (%)	Education (%)	Daily heroin use (gms)	Inject (%)	Heroin use (yrs)
NTORS	1075	29.3	74	n/a	91	88	80	n/a	0.75	62	9
NDTMS/DTORS	77849	29.5	73	n/a	89	85	78	49	0.75	50	9
ISD (Scotland)	7047	30	67	n/a	96	84	83	n/a	0.75	56	>5
ISD (Fife & Tayside)	1441	29	65	n/a	96	86	82	n/a	n/a	58	n/a
Combined HEROIN and METHADONE group	53	26.7	100	3.52	100	87.4	90	54	0.59	75.7	7.5

DTORS=Drug Treatment Outcome Research Study, ISD=Information Services Division or Drug Misuse Prevalence Study, NTORS=National Treatment Outcome Research Study, NDTMS=National Drug Treatment Monitoring System, SIMD=Scottish Index of Multiple Deprivation, %= Percentage, gms=grams in weight; Inject= lifetime injecting, yrs=years, education= completed 12 years of education, Unemp= unemployment, n/a= information not available, n= number of patients, >= more than.

When the combined HEROIN and METHADONE groups recruited were compared to the population studies mentioned above, they did not differ significantly with respect to completing primary and secondary school education ($p=.23$), , daily heroin use ($p=.48$) and chronicity of heroin use ($p=.69$). There was a significant difference in housing with more individuals in the experimental group having a stable accommodation ($p<0.005$), as well as a younger age group ($p=.02$), more unemployment ($p=.04$) and more lifetime injecting ($p=.02$) in the experimental group (Table 3.1).

Table 3.2: Sociodemographic characteristics of the non-completers, non-participants and participants of the HEROIN and METHADONE groups.

	N	Mean age (yrs)	Male (%)	SIMD	Ethnic (% white)	Unem (%)	Stable house (%)	Edu (%)	Daily heroin use (gms)	Injec (%)	Injecting in last 30 days	Heroin use (yrs)
HEROIN group identified	36	25.8	100	3.8	100	90.3	87	53	0.60	62.5	n/a	6.8
HEROIN group recruited	28	26.3	100	3.6	100	88.5	89	50	0.60	60.7	12	6.3
HEROIN group completed	24	26	100	3.6	100	88.5	87	50	0.60	62.5	12	6.1
METHADONE group identified	42	26.6	100	3.5	100	86.4	95	67	0.59	86	0	8.5
METHADONE group recruited	29	27.3	100	3.4	100	86.2	93	58	0.58	89	0	8.8

SIMD=Scottish Index of Multiple Deprivation, Ethnic= ethnicity, Injec= lifetime injecting, %= Percentage, yrs=years, gms=grams in weight, N= patient numbers involved, n/a= information not available, edu= completed 12 years of education, unem= unemployment.

The recruited individuals for both the HEROIN and the METHADONE groups were young with a mean age of 26.7 years, all ethnically white Scottish and living in moderately deprived areas (median SIMD score of 3.5) of Fife or Tayside. Only 54% completed full time primary and secondary education with only 12.7 % employed at the time of the recruitment stage of this study. Most (90%) were living in stable accommodation. The average daily heroin dose was 0.59g which would be a morphine equivalent of 200mg if one is assuming that the heroin was 100% pure with no adulterants present (**Vieweg et al.,2005; Hallenbeck, 2003**). Eighty nine percent of the METHADONE group significantly but subjectively described a lifetime history of injecting heroin ($p<0.001$) when compared to 62.5% of the HEROIN group. There was also a significant difference in the chronicity of heroin use between the HEROIN group (6.1 years) and the METHADONE group (8.8 years) prior to accessing treatment to start methadone stabilisation ($p<0.001$). This information was again not confirmed objectively (**Table 3.2**). There were no significant differences between non-participants, non-completers and cohort participants in all of the sociodemographic characteristics.

Comparison of sociodemographic and clinical characteristics of experimental and control groups

Preliminary analysis of all the experimental and control groups separately indicate that the samples did not come from normally distributed populations with the same standard deviation. A planned (*a priori*) contrasts analysis was therefore run to test for significant differences between the four independent study groups.

A Kruskal-Wallis Test compared the three experimental groups and the healthy control group with each other (describing this process as ‘HEROIN vs METHADONE vs CHRONIC PAIN vs HEALTHY CONTROL groups’). The result showed that the four groups differed with respect to:

(A) NART, age in years, employment, years in education, SIMD, and Fagerström total score from the sociodemographic characteristics.

(B) Age when first used alcohol from the drug and alcohol use histories.

To test the null hypothesis of no differences between the four groups a Mann Whitney U test was subsequently done with collapsed groupings using the same above demographic variables in order to determine where these differences lie (Tables 3.3 & 3.4). The collapsed groupings included:

- HEROIN vs METHADONE groups.
- CHRONIC PAIN vs HEALTHY CONTROL groups.
- HEROIN vs CHRONIC PAIN groups.
- METHADONE vs CHRONIC PAIN groups.
- HEROIN vs HEALTHY CONTROL groups.
- METHADONE vs HEALTHY CONTROL groups.

(a) The HEROIN and METHADONE groups did not differ significantly. These groups had a similar (homogenous) drug use history, morphine equivalent dosages, and drug use history 30 days prior to the baseline neuropsychological testing (except the fact

that the HEROIN group where NOT on methadone and the METHADONE group were stable on methadone and so did not take either illicit methadone or heroin) (**Tables 3.3 & 3.4**).

Table 3.3: Comparison of sociodemographic and clinical characteristics of experimental and control groups*

	HEROIN	METHADONE	CHRONIC PAIN	HEALTHY CONTROLS	Sig ¹ . HEROIN vs METHADONE	Sig. ¹ HEROIN vs P/C	Sig. ¹ METHADONE vs P/C
N	24	29	28	28	n/a	n/a	n/a
Ethnicity (% white)	100	100	100	100	n/a	n/a	n/a
Age (yrs)	26.3 (3.45)	27.3 (2.34)	33.97 (4.35)	24.12 (3.56)	p=.38	H >P = p<0.001	M >P/C = p<0.005
R:L	23:1	28:1	27:2	28:0	n/a	n/a	n/a
SIMD	3.6(1.9)	3.41 (1.4)	4.6(2.00)	5.9 (2.5)	p=.72	H >C = p<0.001	M >P p<0.01, M>C = p<0.001
Unemployed (%)	87.5	86.2	50	0	p=.86	P<0.001	p<0.001
Stable accommodation (%)²	87	93	100	92.8	p=.67		M >P = p<0.005
Education (yrs)	10.8(1.5)	10.6 (2.3)	11.18 (1.22)	15.4 (2.1)	p=.57	H >C = p<0.001	H>C = p<0.001
Fagerström total score	5.2 (2.7)	4.5 (2.7)	1.3(1.9)	0.04 (0.2)	p=.41	p<0.001	p<0.001
NART (IQ)	106.1 (12.2)	108.9 (7.6)	115.9 (4.9)	118.3 (5.1)	p=.92	p<0.001	C>M = p<0.001 P>M= p<0.01)

Sig ¹= significance at p<0.01 two tailed, ²Stable accommodation = own house + rented accommodation + living with parents (excluded hostel, student and homeless), *=mean total scores (+/- standard deviation), P=CHRONIC PAIN Group, C=HEALTHY CONTROL Group, H= HEROIN Group, M= METHADONE Group, n/a =not applicable, yrs=years; R:L= Right: Left Handedness, SIMD= Scottish Index of Multiple Deprivation, NART= National Adult Reading Test, IQ= Intelligence Quotient, %= percentage, ns=not significant, N=Total number in group.

Table 3.4: Comparative drug and alcohol use histories (self reported) in experimental and control groups.*

	HEROIN	METHADONE	CHRONIC PAIN	HEALTHY CONTROLS	Sig. ¹ HEROIN VS METHADONE	Sig. ¹ HEROIN vs P/C	Sig. ¹ M vs P/C
Daily intake expressed as morphine equivalent dose (mg)* ¹	184.5 (82.1) (n=24)	147.4 (59.3) (n=29)	59.1(46.8) (n=28)	n/a	p=.09	H >P = $p<0.001$	M>P = $p<0.001$
Age when first used heroin (yrs)	19.4 (4.1) (n=24)	17.9 (2.6) (n=29)	n/a	n/a	p=.46	n/a	n/a
Age when using opioids regularly (yrs)	20.2 (3.7) (n=24)	19.5 (2.8) (n=29)	n/a	n/a	P=.63	n/a	n/a
Age when dependent on opioids	20.9 (3.9) (n=24)	19.9(2.8) (n=29)	n/a	n/a	p=.49	n/a	n/a
Age when injecting opioids	20.5 (4.0) (n=17)	19.1 (6.0) (n=29)	n/a	n/a	p=.02	n/a	n/a
Years of opioid use	6.1 (2.9) (n=24)	8.8 (2.8) (n=29)	5.0 (2.3) (n=28)	n/a	M>H = $p<0.001$	p=.21	M>P = $p<0.001$
Stable methadone use (years)	n/a	1.3 (0.5) (n=29)	n/a	n/a	n/a	n/a	n/a
Days of illicit methadone in last 30 days	1.8(3.7) (n=10)	n/a	n/a	n/a	n/a	n/a	n/a
Days of heroin use in last 30 days	29.5(2.7) (n=24)	0.8 (3.9) (n=3)	n/a	n/a	n/a	n/a	n/a
Age when first used benzodiazepine (years)	16.82(3.3) (n=17)	16.2 (3.5) (n=17)	n/a	n/a	p=.18	n/a	n/a
Days of benzodiazepine use in the last 30 days	3.0(4.6) (n=12)	3.2 (0.8) (n=4)	0.1 (0.8) (n=1)	n/a	p=.88	H>P = $p<0.001$	p=.19
Age when first used Cocaine (years)	17.7 (2.3) (n=10)	18.1 (2.5) (n=9)	n/a	n/a	p=.49	n/a	n/a
Days of cocaine use in last 30 days	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Age when first used cannabis (years)	12.83(1.6) (n=23)	12.9 (1.4) (n=29)	26.0(10.3) (n=5)	n/a	p=.49	H >P = $p<0.001$	M >P = $p<0.001$
Days of cannabis use in last 30 days	12.3(13.4) (n=15)	14.7 (14.2) (n=18)	2.9 (8.0) (n=5)	n/a	p=.75	H>P = $p<0.001$	M>P = $p<0.001$
Age when first used alcohol (years)	12.5(1.3) (n=24)	12.7(1.9) (n=29)	15.2(1.2) (n=28)	14.7 (0.6) (n=28)	p=.89	H>C = $p<0.001$	M>C = $p<0.001$
Days of alcohol use in last 30 days	2.2(6.1) (n=10)	4.0(4.9) (n=15)	5.1(8.3) (n=17)	4.0 (6.3) (n=17)	p=.14	p=.06	p=.83

Sig¹= significance at $p<0.01$, *=mean total scores (+/- standard deviation), n/a= not applicable, P=Chronic Pain Group, C=Healthy Control Group, H= Heroin Group, M= Methadone Group, n=number in group analysed, yrs=years, n= number of individuals analysed, mg=milligrammes, *¹= morphine equivalent with heroin purity of 40%.

(b) Groups with no history of illicit substance misuse and no opioid dependence (CHRONIC PAIN and HEALTHY CONTROLS) where compared. Analysis showed significant differences with the CHRONIC PAIN group being older ($p<0.001$), more

unemployed ($p<0.001$), less educated ($p<0.001$), and more dependent on nicotine ($p<0.001$) than the HEALTHY CONTROL group. Both groups were similar in SIMD ($p=.10$), accommodation status ($p=.12$) and NART ($p=.07$).

(c) The opioid dependent groups (HEROIN and METHADONE) were different from either the CHRONIC PAIN or HEALTHY CONTROL groups in most of the sociodemographic and substance misuse history domains. The nature and consequences of substance misuse was most obvious when one looked at current nicotine use and dependence status which showed that all individuals in the HEROIN group, and all but one individual in the METHADONE group smoked. This compared with only one individual in the HEALTHY CONTROLS who smoked. First initiation to alcohol use also showed a tendency for the HEROIN and METHADONE groups starting about two years earlier than the CHRONIC PAIN and/or the HEALTHY CONTROL groups (**Tables 3.3 & 3.4**).

In summary NART, age in years, Fagerström total score and past alcohol use have been used as co-variables for further analysis of all the four groups.

Comparison of sociodemographic and clinical characteristics of the intra-cohort groups

Further Mann Whitney U test was done with intra-cohort groupings using the above demographic variables in order to determine where, if any, differences lie between the following groups:

- HEROIN group: Between participants who experienced lower third ($n=8$) and upper third ($n=8$) levels of the opioid withdrawal scale (COWS) scores.
- METHADONE group: Between participants tested at baseline ($n=29$) and then followed up after 6 months ($n=18$).
- INJECTING: Between participants with a lifetime subjective history of injecting illicit opioids ($n=41$) and others with no history of injecting ($n=11$). These groups were selected from the HEROIN and METHADONE groups.

(a) When the participants from the HEROIN group with a Clinical Opiate Withdrawal Scale (COWS) of between 8-14 (lower 8) were compared with the same HEROIN cohort with COWS of 18-25 (upper 8) it did not differ significantly with respect to age ($p=.88$), SIMD score ($p=.75$), years in education ($p=.38$), years when starting using alcohol ($p=.07$), alcohol amount used in last month ($p=.87$), current smoking dependence (Fagerström scores) ($P=.96$) and NART ($p=.02$).

(b) There were no significant differences between the 29 participants of the METHADONE group at baseline and the 18 participants from the same METHADONE group followed up after six months (**Table 3.5 & 3.6**).

Table 3.5: Group descriptions of sociodemographic characteristics*.

	METHADONE group at initial testing session	METHADONE group after 6 months from baseline	Sig. ¹
N	29	18	n/a
Ethnicity (% white)	100	100	n/a
SIMD	3.4 (1.4)	3.6 (1.7)	$p=.22$
Age (yrs)	27.3 (2.3)	27.4 (2.1)	$p=.82$
R:L	28:1	18:0	n/a
% unemployed	86.2	83.3	$p=.85$
% stable accommodation²	93	88.8	$p=.16$
Yrs in education	10.6 (2.2)	10.8 (2.4)	$p=.87$
Fagerström total score	4.5 (2.7)	5.4 (2.3)	$p=.03$
NART (IQ)	108.9 (7.6)	106.9 (7.7)	$p=.07$

*Sig¹ = significance at $p<0.01$, ²Stable accommodation = own house + rented accommodation + living with parents (excluded hostel, student and homeless), * = mean total scores (+/- standard deviation), M = METHADONE Group, n/a = not applicable, yrs = years; R:L = Right: Left Handedness, SIMD = Scottish Index of Multiple Deprivation, NART = National Adult Reading Test, IQ = Intelligence Quotient, % = percentage, N = Total number in group.*

Table 3.6: Comparative drug and alcohol use histories.*

	METHADONE group at initial testing session (N=29)	METHADONE group after 6 months from baseline (N=18)	Sig. ¹
Morphine equivalent dose(mg)* ¹	147.4 (59.3) (n=29)	154.9 (48.7) (n=18)	p=.40
Age when first used heroin (yrs)	17.9 (2.6) (n=29)	18.3 (2.6) (n=18)	p=.25
Age when first used other opioids (yrs)	16.8 (2.1) (n=29)	16.7 (2.1) (n=18)	p=.89
Age when using opioids regularly (yrs)	19.5 (2.8) (n=29)	20.1 (3.1) (n=18)	p=.14
Age when dependent on opioids (yrs)	19.9 (2.8) (n=29)	20.5 (3.1) (n=18)	p=.49
Age when injecting opioids	19.1 (6.0) (n=11)	21.0 (3.1) (n=8)	p=.06
Opioid use (yrs)	8.8 (2.8) (n=29)	9.39 (2.9) (n=18)	p=.18
Stable methadone use (yrs)	1.3 (0.5) (n=29)	1.2 (4.9) (n=18)	p=.22
Days of illicit methadone in last 30 days	n/a	n/a	n/a
Days of heroin use in last 30 days	0.8 (3.9) (n=2)	0.05 (0.2) (n=4)	p=.31
Age when first used benzodiazepine(yrs)	16.2 (3.5) (n=28)	15.2 (1.8) (n=18)	p=.66
Days of benzodiazepine use in the last 30 days	0.2 (0.8) (n=2)	0.1 (0.4) (n=4)	p=.52
Age when first used Cocaine (yrs)	18.1 (2.5) (n=11)	19.0 (2.5) (n=18)	p=.84
Days of cocaine use in last 30 days	n/a	n/a	n/a
Age when first used cannabis (yrs)	12.9 (1.4) (n=29)	13.2 (1.5) (n=18)	p=.26
Days of cannabis use in last 30 days	14.7 (14.2) (n=29)	11.28 (14.1) (n=18)	p=.81
Age when first used alcohol(yrs)	12.7 (1.9) (n=29)	12.83 (2.2) (n=18)	p=.82
Days of alcohol use in last 30 days	4.0 (4.9) (n=29)	4.00 (4.9) (n=18)	p=.62

Sig¹= significance at $p < 0.01$, *=mean total scores (+/- standard deviation), n/a= not applicable, n=number in group analysed, yrs=years, mg=milligrams, N=total number in study group, *¹= morphine equivalent assuming 40% heroin purity.

(c) There were no significant differences in most characteristics when the 43 injecting opioid dependent participants from both the HEROIN and METHADONE groups were compared with the 10 non- injecting participants from the same collapsed grouping.

The NART score was the only variable to be significantly in favour to the injecting group ($p<0.01$) (**Tables 3.7 & 3.8**). Therefore NART has been used as a co-variate for further analysis of this grouping

Table 3.7: Group descriptions of sociodemographic characteristics* between INJECTING and non- injecting groups within the opioid dependent cohorts.

	Injecting	Non-Injecting	Sig ¹
N	43	10	n/a
Ethnicity (% white)	100	100	n/a
SIMD	3.42 (1.48)	3.90 (2.02)	$p=.41$
Age (yrs)	26.85(2.79)	26.86(3.51)	$p=.83$
R:L	20:1	9:1	$p=.51$
% unemployed	88.4	80	$p=.47$
% stable accommodation²	88.4	90	$p=.20$
Yrs in education	10.56 (2.0)	11.10 (1.37)	$p=.61$
Fagerström total score	4.95 (2.80)	4.20 (2.89)	$p=.48$
NART (IQ)	109.33(8.93)	100.30(11.20)	$p<0.01$

Sig¹= significance at $p<0.01$, ²stable accommodation = own house + rented accommodation + living with parents (excluded hostel, student and homeless), *=mean total scores (+/- standard deviation), n/a =not applicable, yrs=years; R:L= Right: Left Handedness, SIMD= Scottish Index of Multiple Deprivation, NART= National Adult Reading Test, IQ= Intelligence Quotient, %= percentage, N=Total number in group, %= percentage.

Table 3.8: Comparative drug and alcohol use histories*.

	Injecting (N=43)	Non- Injecting (N=10)	Sig. ¹
Morphine equivalent dose(mg)*¹	174.62(72.89)	119.48(51.61)	p=.02
Age when first used heroin (yrs)	18.16(3.07) (n=43)	20.3 (4.37) (n=10)	p=.28
Age when first used other opioids (yrs)	18.0 (2.88) (n=7)	n/a (n=0)	n/a
Age when using opioids regularly (yrs)	19.55 (3.09) (n=43)	21.0 (3.74) (n=10)	p=.26
Age when dependent on opioids (yrs)	20.14 (3.55) (n=43)	21.1 (3.58) (n=10)	p=.41
Age when injecting opioids	20.58 (3.35) (n=43)	n/a	n/a
Opioid use (yrs)	7.81 (3.03) (n=43)	6.6 (3.56) (n=10)	p=.34
Age when first used methadone use (yrs)	22.7 (2.77) (n=30)	26.0 (3.83) (n=4)	p=.04
Days of illicit methadone in last 30 days	0.37 (0.98) (n=17)	2.7 (5.44) (n=7)	p=.21
Days of heroin use in last 30 days	11.72 (14.59) (n=16)	22.1 (5.44) (n=7)	p=.04
Age when first used benzodiazepine(yrs)	16.07 (2.97) (n=27)	18.14 (4.48) (n=7)	p=.14
Days of benzodiazepine use in the last 30 days	1.07 (2.84) (n=17)	3.4 (4.99) (n=7)	p=.24
Age when first used Cocaine (yrs)	17.87 (2.53) (n=16)	18.0 (0.00) (n=3)	p=.42
Days of cocaine use in last 30 days	n/a	n/a	n/a
Age when first used cannabis (yrs)	12.76 (1.47) (n=43)	13.3 (1.42) (n=10)	p=.18
Days of cannabis use in last 30 days	13.33 (13.66) (n=21)	13.2 (14.71) (n=8)	p=.94
Age when first used alcohol(yrs)	12.67 (1.79) (n=43)	12.3 (0.83) (n=10)	p=.27
Days of alcohol use in last 30 days	3.58 (5.77) (n=28)	1.4 (4.09) (n=10)	P=.07

Sig ¹= significance at p<0.01, *=mean total scores (+/- standard deviation), n/a= not applicable, n=number in group analysed, yrs=years, mg=milligrams, N=total number in study group, *¹= morphine equivalent assuming 40% heroin purity.

Chapter 4: Results-Neuropsychological functioning in men with a history of chronic opioid use: Impulsivity

Background

Impulsivity may be defined as '*a predisposition toward rapid, unplanned reactions to internal or external stimuli with diminished regard to the negative consequences of these reactions for the impulsive individual or to others*' (Chamberlain & Sahakian, 2007; Potenza, 2007). Impulsivity encompasses behaviours that are rash, poorly planned, or focus on short-term outcomes despite potentially negative consequences in the long-term (Ainslie, 1975; Dawe and Loxton, 2004; Dawe *et al.*, 2004). It is a multiple component construct (Lane *et al.*, 2003; Reynolds *et al.*, 2006; Reynolds, 2006) with three broad classes of neuropsychological tests used to measure impulsivity. They include cognitive impulsivity, motor impulsivity and non-planning impulsivity (Table 4.1 and Chapter 1 & 2).

Cognitive impulsivity involves making quick but disadvantageous decisions (Olmstead, 2006). The decisions of more impulsive individuals are influenced by preferring to choose a small reward available immediately (or after a short delay) over a larger reward available at some point in the future (Bickel & Marsch, 2001; Reynolds, 2006, Kirby *et al.*, 1999). The terms sensation seeking, urgency (Whiteside & Lynam, 2001) or delay-discounting (Mischel *et al.*, 1989) are other terms that describe cognitive impulsivity.

Table 4.1: Impulsivity domains:

Main Domain	Subtypes	Other names	Definition	Examples of test
Cognitive Impulsivity	Reflection Impulsivity	Delay Discounting or Urgency	Lack of premeditation and inability to gather and evaluate information	IGT, MFFT, BIS,GDT,DDT, CGT, RDMT
	Risk Taking	Sensation Seeking		CGT, IGT, RDMT
Motor Impulsivity		Inhibitory Control	Ability to suppress emotional, cognitive and behavioural responses	
	Behavioural Inhibition	Motor Response Inhibition	Process requires to stop a planned movement	AGN,SS,Go/NoGo
	Cognitive Inhibition	Focused Attention	Process in which individuals are required to suppress a salient but conflicting stimulus while identifying less salient ones	ST
Non-Planning Impulsivity	Reasoning and Problem Solving	Central Executive (Working Memory)	Ability to think ahead and actively search for an appropriate solution AND ability to opt for larger delayed rewards over smaller more immediate rewards	TOL, SOC, ROCFT, TOH, PMT,WAIS –III (Block Design, Matrix Reasoning), SSP, SWM

AGN= *Affective Go-NoGo (CANTAB)* , BIS= *Barratt Impulsivity Scale* , CGT= *Cambridge Gambling Task (CANTAB)*, DDT= *Delay Discounting Test*, GDT= *Game and Dice Test*, IGT= *Iowa Gambling Task*, MFFT= *Matching Familiar Figures*, PMT= *Proteus Maze Test*, RDMT= *Rogers Decision Making Task*, ROCFT= *Rey-Osterreith Complex Figure Test*, SOC= *Stockings of Cambridge (CANTAB)*, SSP= *Spatial Span (CANTAB)*, SS= *Stop Signal* ,SWM= *Spatial Working Memory (CANTAB)*, ST= *Stroop Test* , TOH= *Tower of Hanoi*, TOL= *Tower of London (CANTAB)*, WAIS-III= *Weschler Adult Intelligence Scale Third Edition*.

A series of studies have suggested that both licit and illicit substance using populations show significantly higher rates of cognitive impulsivity, compared to non substance using controls (Kollins, 2003; Baker *et al.*, 2003; Petry, 2002; Monterosso *et al.*, 2001, Mitchell *et al.*, 2002). Impaired cognitive impulsivity was also reported in opioid dependent (Clark *et al.*, 2006) and methadone using (Rotheram-Fuller *et al.*, 2004) populations. However abstinent heroin users were also found to discount

significantly higher than non substance using controls (**Mintzer *et al.*, 2005**). This is especially relevant in suggesting that cognitive impulsivity may be conceptualized as trait-like and not simply due to direct effect of opioid or other substance dependence (**de Wit, 2009; Ersche *et al.*, 2010**). Impulsive behaviours are closely linked to substance use and abuse, both as contributors and as consequences of substance use. Trait impulsivity is an important determinant of substance use during development, and impulsive behaviour may increase the likelihood of substance use, dependence and/or relapse after a period of abstinence (**Koob & Volkow, 2010**). However, these effects depend on the behavioural measure used to assess impulsivity (**de Wit, 2009; Everitt *et al.*, 2008**) and it remains unclear to what extent impulsive behaviour especially cognitive impulsivity is 'state' dependent or an individual trait (**Rose *et al.*, 1996; Davis *et al.*, 2002**).

In another study, a buprenorphine treated group performed significantly better than those participants maintained on methadone and a non- substance using healthy control group in the cognitive impulsivity tasks (**Pirastu *et al.*, 2006**). This study indicated that specific opioids might have differential effects on cognitive impulsivity. This observation is limited by the fact that such groups were prescribed different opioids due to their differences in their dependence status, perhaps due to different substance use careers with one population exposed to less risk than the other, or that the different populations experiencing different vulnerability trait factors to sensation seeking (Chapter 1).

There are inconsistencies in substance users' cognitive impulsivity or decision making on the Iowa Gambling Task (IGT) across studies. Whilst studies did not find a measurable impairment in cognitive impulsivity in opioid and polysubstance users (**Adinoff *et al.*, 2003; Ernst *et al.*, 2003; Mintzer *et al.*, 2005**) others found increased cognitive impulsivity (or impaired decision making) outcomes in these groups of substance users compared with non- substance using healthy controls (**Bechara *et al.*, 2002b; Rotheram-Fuller *et al.*, 2004; Pirastu *et al.*, 2006**). However such impaired decision making performance has also been identified in other clinical non- substance

dependent groups, for example, in suicide attempters (**Jollant *et al.*, 2005**) and psychopathic individuals (**Mitchell *et al.*, 2002; van Honk *et al.*, 2002**). In **Vassileva *et al.*, (2007)** eighteen psychopathic opioid users, based on their scores on the Revised Hare Psychopathy Checklist (PCL-R), consistently showed impaired decision making outcomes whilst the sixty non-psychopathic opioid users successfully adjusted their decision- making outcomes in the course of the task toward the advantageous tasks (**Hare, 1991**).

These findings have also been observed in studies using the Cambridge Gambling Task (CGT) when chronic opioid users were compared to chronic amphetamine users (**Ersche *et al.*, 2005a & 2005b; Rogers *et al.*, 1999a**). Chronic amphetamine users, overall, selected the small immediate reward option less frequently (i.e., in only 85% of trials) than chronic opioid users (92%) and controls (95%) (**Rogers *et al.*, 1999a**). Even though the amphetamine users chose disadvantageously, they neither increased their gambles on the less favourable options nor did they significantly choose against the odds on the risky conditions. Disadvantageous decision-making outcomes in amphetamine users on the CGT appears to be due to impairment in correctly estimating outcome probabilities and may not reflect a reward-seeking strategy *per se* (**Ersche *et al.*, 2006a**).

Impairment in motor impulsivity (**Olmstead, 2006; Barratt, 1985**) occurs when individuals have difficulty in suppressing reward-driven automatic behaviour or pre-potent responses (**Logan *et al.*, 1997**). Motor impulsivity is assessed by observing (a) behavioural (or motor) response inhibition (e.g. through the Go-NoGo Tasks) (**Newman *et al.*, 1990**) and (b) cognitive inhibition (e.g. through the Stroop Test (ST)) (**Stroop, 1992**) (**Table 4.1**).

In contrast to the accumulating evidence for behavioural response inhibition impairments in populations who use other drugs, such as in chronic psychostimulant users, (**Hester & Garavan, 2004; Hester *et al.*, 2007; Monterosso *et al.*, 2005**), the majority of the limited but methodologically sound opioid related studies did not find

behavioural inhibition impairments in either the methadone users (**Rounsaville *et al.*, 1982; Passetti *et al.*, 2008**) or in the abstinent heroin users (**Verdejo-Garcia *et al.*, 2007b**). Consistent with the above opioid related studies the ability to suppress a salient but conflicting stimulus while identifying a less salient one (cognitive inhibition) was also not compromised in methadone users (**Prosser *et al.*, 2006**).

Non-planning impulsivity is the ability to 'think ahead' and to actively search for an appropriate solution. It is considered as an essential part of goal directed behaviour (**Owen, 1997**). This neuropsychological domain also includes the central executive component of the working memory (**Baddeley, 1986**) as assessed with the Spatial Working Memory (SWM) task from the CANTAB test battery (**Downes *et al.*, 1989**).

In a study by **Clark *et al.* (2006)** opioid dependent users not only reported higher overall levels of impulsivity compared with non-substance using controls, they also scored higher on the non-planning impulsivity subscale of the Barratt Impulsiveness Scale-11 (BIS) (**Patton *et al.*, 1995**). Opioid dependent users also significantly solved fewer problems correctly on the one-touch Tower of London (TOL) (**Owen *et al.*, 1995**), and needed more attempts in order to generate correct answers compared to non- substance using controls (**Ersche *et al.*, 2006a; Ornstein *et al.*, 2000**) even though they took as long to answer as did the controls (i.e. no impairment in motor impulsivity). **Fishbein *et al.* (2007a)** tested abstinent heroin users with the Stockings of Cambridge (SOC) task from the CANTAB test battery (**Downes *et al.*, 1989**), with similar results. In contrast methadone users (**Passetti *et al.*, 2008**) and abstinent heroin users (**Brand *et al.*, 2008**) tested on the TOL task did not show impairment in non-planning impulsivity when compared with non-substance using healthy controls. This inconsistency could be related to the clinical characteristics of the opioid cohorts tested (e.g. after inpatient opioid detoxification vs initiation of methadone community treatment) and the lack of methodological clarity to differentiate neuropsychological effects due to either acute or subacute use from those of chronic opioid exposure (**Chapters 1 & 2 and Table 4.2**).

Table 4.2: Chronic opioid use and impulsivity. Previous research findings.*

Neuropsychological domain	Illicit chronic heroin use	Abstinent ex-heroin use	Methadone use	Other opioids ¹	Chronic opioid dependence
Cognitive Impulsivity (reflection impulsivity)		Mintzer <i>et al</i> (2005)↓ Verdejo-Garcia <i>et al</i> (2007 a)↓	Pirastu <i>et al</i> (2006)↓ Rotheram-Fuller <i>et al</i> (2004)↓	Pirastu <i>et al</i> (2006)↑	Clark <i>et al</i> (2006)↓
Cognitive Impulsivity (risk taking)	Ersche <i>et al</i> (2005)↔	Fishbein <i>et al</i> (2007)↓ Fishbein <i>et al</i> (2005)↓ Clark <i>et al</i> (2006)↓	Passeti <i>et al</i> (2008)↓		Rogers <i>et al</i> (1999)↓ Ersche <i>et al</i> (2005) ↔
Motor Impulsivity (behavioural or motor response inhibition)	McNairy <i>et al</i> (1984)↓	Verdejo-Garcia <i>et al</i> (2007b)↔ Verdejo-Garcia <i>et al</i> (2007a)↓	Rounsaville <i>et al</i> (1982)↔ Passeti <i>et al</i> (2008)↔ Specka <i>et al</i> (2000) ↓	Sjogren <i>et al</i> (2005)↓ Vainio <i>et al</i> (1995)↔ Schindler <i>et al</i> (2004)↔	
Motor Impulsivity (cognitive Inhibition)			Prosser <i>et al</i> (2008)↔		
Non-Planning Impulsivity		Fishbein <i>et al</i> (2007)↔ Brand <i>et al</i> (2008)↔	Passeti <i>et al</i> (2008)↔	Vainio <i>et al</i> (1995)↔ Schindler <i>et al</i> (2004)↔	Ersche <i>et al</i> (2006)↓ Ornstein <i>et al</i> (2000)↓ Clark <i>et al</i> (2006)↓

*= $p < 0.05$; ↔ = no difference in neuropsychological (impulsivity) performance; ↓ = neuropsychological (impulsivity) deficits present; ↑ = improvement in neuropsychological (impulsivity) performance when compared to healthy controls, other opioids ¹ = buprenorphine, morphine, oxycodone and/or tramadol.

In summary, the accumulated evidence is inconsistent and limited. Chronic consumption of opioids might be worsening an underlying trait for poor quality of decision making, especially cognitive impulsivity, with different subgroups of opioid dependent populations expressing different quality of risk. However there is limited evidence that chronic heroin and methadone use causes deficits in motor or non-planning impulsivity (**Table 4.2**).

There are a variety of confounding variables, such as age (**Deakin *et al.*, 2004**), differences in intelligence quotient (**Fishbein *et al.*, 2005a, 2005b**), co-morbid psychiatric illness (**Jollant *et al.*, 2005; Jollant *et al.*, 2007**), and co-morbid personality

disorder (**Leland & Paulus, 2005**), amongst others, as described in Chapter 1 of this thesis, which may exacerbate the presence or absence of impulsivity in individuals with chronic opioid dependence.

In light of the previous research in the area of opioid dependent use and neuropsychological functioning, the present study set out to expand on the current limited knowledge base by comparing the neuropsychological performance of chronic heroin dependent users, methadone maintained male participants and others taking opioid for chronic pain compared to non-substance using healthy controls as explained in Chapter 3 of this thesis. This will help test the hypothesis (1):

(1) Is chronic opioid dependence associated with neuropsychological impairment reflected in altered performance on measures of impulsivity and risk taking?

At least three factors have been identified as related to drug taking that may exert an important influence over neuropsychological performance;(1) duration of opioid use, (2) level of opioid receptor occupancy during behavioural testing (a) during intoxication, (b) during withdrawal and (c) during a stable methadone maintenance and (3) injecting status.

Clinical studies suggest that with increasing duration of heroin use comes increased tolerance, which means that increasing doses are required to reduce or abolish physical cravings and to prevent opioid withdrawal symptoms (**Jasinski, 1997**). Therefore, as duration of use increases, the dose required to avoid withdrawal is predicted to increase (**Martin & Jasinski, 1969**). A shift from smoking to injecting opioid is a phenomenon that is closely linked to opioid dependence. Similarly, individuals who use higher doses of heroin will generally require higher doses of methadone to prevent opioid withdrawal symptoms (**Olmedo & Hoffman, 2000**). This means that these three factors; duration of use, state of intoxication or withdrawal and injection status are related to each other. However the evidence relating to the

influence of any of these factors on neuropsychological functioning is limited and inconsistent. Therefore the next two related hypothesis (2 and 3) to test are:

(2) In patients with chronic opioid dependence, is injection status associated with neuropsychological impairment as reflected in altered performance on measures of impulsivity and risk taking?

(3) In patients with chronic opioid dependence is the degree of acute opioid exposure (acute intoxication, withdrawal or stable initial exposure to methadone), or duration of opioid exposure (period of methadone maintenance) associated with neuropsychological impairment as reflected in altered performance on measures of impulsivity and risk taking?

Statistical considerations

Basic statistical considerations have been described in Chapter 2. The data from the CGT, AGN, SWM and SSP tasks met assumptions of normality and homogeneity of variance. The SOC did not meet this assumption and to stabilise variance and diminish *skewness* and *kurtosis*, SOC data were subjected to square root (*SQRT*) transformation (**Fields, 2009**).

Testing hypothesis 1 and 2

Data were initially analysed using univariate or repeated measures ANCOVA with a *between subjects factor* of GROUP (HEROIN vs. METHADONE vs. CHRONIC PAIN vs. HEALTHY CONTROL) and NART, age in years, SIMD, total Fagerström score, years in education and past alcohol use in years as covariates.

Further *a priori* subgroup analyses were conducted using (1) a two-group factor reflecting DEPENDENCE status (HEROIN and METHADONE groups vs. CHRONIC PAIN and HEALTHY CONTROL groups) and (2) a two-group factor reflecting INJECTING status (HEROIN and METHADONE injecting vs. HEROIN and METHADONE never injecting groups) separately as *between subject factors*.

Behavioural data on the CGT were further analysed using mixed-model analysis of variance (ANCOVA) with GROUP (HEROIN vs METHADONE vs CHRONIC PAIN vs HEALTHY CONTROL) as a *between-subjects fixed factor*, and *direction* (Ascend, Descend) and *difficulty* (ratio 9:1, 8:2, 7:3, and 6:4) as *within-subjects factors*. A clustering technique utilising repeated measures ANCOVA that allowed comparison between all difficulty levels on both condition levels was used. Trials with a 5:5 ratio of red-blue boxes were included in the task design to ensure that participants perceived the task as a random trial sequence.

Between-group effects in the ANCOVA models were analysed as follows. A planned comparison between the HEALTHY CONTROL and three experimental groups (HEROIN, METHADONE and CHRONIC PAIN) was used to detect any difference in performance. In this four-group model, significant *between-group effects* were investigated using pair-wise comparisons with *Bonferroni* correction procedure. Effect sizes for the group comparisons were calculated using Cohen's *d*, i.e. the difference between the means divided by the pooled SD (Cohen, 1988).

Testing hypothesis 3

Repeated measures ANCOVA was used to evaluate CGT, AGN, SWM, SSP and SOC performance between the HEROIN group participants at baseline (whilst on illicit heroin), in controlled opioid withdrawal and subsequently when stabilised on methadone according to the tolerance testing procedure protocol with presumed *opioid receptor occupancy state* as a *within subject factor* to determine whether performance on any of these tasks was modified by different degrees of opioid receptor occupancy (heroin, withdrawal and stable on methadone).

Similarly repeated measures ANCOVA was performed for the METHADONE group at baseline and at 6 months follow up with *duration* as a *within subject factor* to determine whether any aspects of performance improved or deteriorated with time and continued exposure to chronic, sustained released opioid (methadone).

The homogeneity of variance across groups in repeated-measures design ANCOVAs was assessed by the Mauchly Sphericity Test (**Mauchly, 1940**). Where data sets significantly ($p < 0.05$) violated this requirement for a repeated-measures design ANCOVA, the Greenhouse Geisser Epsilon (ϵ) correction parameter for degrees of freedom (**Greenhouse & Geisser, 1959; Winer *et al.*, 1991**) was used to calculate a more conservative p value for each F ratio.

Results

All subjects completed all of the tests. Mean performance (not adjusted for covariates), statistical comparisons and effect sizes (d) for the HEROIN, METHADONE, CHRONIC PAIN and HEALTHY CONTROL groups, are summarised in **Table 4.3a, b & c**.

Table 4.3a : Summary of baseline neuropsychological findings for cognitive impulsivity (not adjusted for covariates).

Cognitive Impulsivity	HEROIN N= 24	METHADONE N= 29	CHRONIC PAIN N= 28	HEALTHY CONTROL N= 28		
	Mean (s.d)	Mean (s.d)	Mean (s.d)	Mean (s.d)	Sig.	d
CGT						
Quality of Decision	0.83 (0.21)	0.91 (0.09)	0.93 (0.10)	0.96 (0.06)	C>H**	0.84
Deliberation Time	2826.92(1365.51)	3386.89 (1762.26)	2676.23(766.70)	2128.49(350.74)	C<M***	0.99
Risk taking	0.58 (0.18)	0.64 (0.11)	0.52 (0.13)	0.58 (0.08)	NS	
Overall Proportion Bet	0.55 (0.17)	0.59 (0.10)	0.50 (0.13)	0.53 (0.08)	C<H** P<H**	0.14 0.36
Delay Aversion	0.43 (0.23)	0.31 (0.19)	0.32 (0.23)	0.25 (0.14)	C<H*	0.95
Risk Adjustment	0.72 (0.71)	1.00 (0.78)	1.08 (0.73)	1.72 (0.76)	C>H*** C>M**	1.36 0.94

d = effect size, Sig = Significance; * = $p < 0.01$, ** = $p < 0.005$, *** = $p < 0.001$, NS = no significant impairment in neuropsychological outcomes with $p < 0.01$, H = HEROIN Group, P = CHRONIC PAIN Group, M = METHADONE Group, C = HEALTHY CONTROL Group.

Table 4.3b : Summary of baseline neuropsychological findings for motor impulsivity (not adjusted for covariates).

Motor Impulsivity	HEROIN N= 24	METHADONE N= 29	CHRONIC PAIN N= 28	HEALTHY CONTROL N= 28		
	Mean (s.d)	Mean (s.d)	Mean (s.d)	Mean (s.d)	Sig.	d
Affective Go-NoGo (AGN)						
Total Commission Errors	16.37 (11.95)	11.28 (8.32)	6.96 (6.17)	6.36 (4.82)	P<H*** C<H***	1.10
Commission Errors (shift)	8.25 (6.66)	5.52 (4.52)	3.50 (3.28)	3.18 (2.59)	C<H**	1.00
Commission Errors (non-shift)	8.12 (5.94)	5.24 (4.08)	3.46 (3.50)	3.18 (2.82)	C<H***	1.06
Commission Errors (positive)	7.87 (6.67)	5.17 (4.15)	4.14 (3.61)	3.64 (3.08)	C<H*	0.81
Commission Errors (negative)	8.50 (6.12)	5.59 (4.29)	2.82 (3.02)	2.71 (2.65)	C<H***	1.23
Total Omissions Errors	12.75 (10.30)	19.90 (25.16)	7.86 (13.22)	6.54 (14.64)	NS	
Omission Errors (shift)	6.04 (5.02)	9.48 (12.86)	3.71 (6.68)	3.25 (7.15)	NS	
Omission Errors(non-shift)	6.71 (5.68)	9.96 (12.53)	4.14 (6.73)	3.29 (7.56)	C<H*	0.51
Omission Errors (positive)	5.79 (5.15)	10.41 (12.64)	4.32 (6.67)	3.57 (7.37)	NS	
Omission Errors (negative)	6.96 (5.89)	9.03 (12.83)	3.54 (6.93)	2.96 (7.38)	NS	
Mean Correct Latency	524.88 (77.30)	533.20 (92.26)	530.07 (62.65)	495.46 (65.99)	NS	

d= effect size, Sig =Significance, *= $p<0.01$, **= $p<0.005$, *** = $p<0.001$, NS= no significant impairment in neuropsychological outcomes with $p<0.01$, H=HEROIN Group, P= CHRONIC PAIN Group, M= METHADONE Group, C=HEALTHY CONTROL Group.

Table 4.3c : Summary of baseline neuropsychological findings for non-planning impulsivity
(not adjusted for covariates).

Non-Planning Impulsivity	HEROIN N= 24	METHADONE N= 29	CHRONIC PAIN N= 28	HEALTHY CONTROL N= 28		
	Mean (s.d)	Mean (s.d)	Mean (s.d)	Mean (s.d)	Sig.	d
Stocking of Cambridge (SOC) (SQRT)						
Problem solved in minimum number of moves (2 moves)	1.47 (0.14)	1.41 (0.00)	1.43 (0.09)	1.41 (0.00)	NS	
Problem solved in minimum number of moves (5 moves)	2.59 (0.22)	2.62 (0.28)	2.65 (0.28)	2.41 (0.19)	C<H * C<M***	0.80 0.87
Mean Initial Thinking Time (2 moves)	38.74 (24.45)	51.48 (23.24)	38.82 (21.49)	36.94 (25.69)	NS	
Subsequent Thinking Time (2 moves)	18.67 (29.65)	5.47 (14.14)	5.04 (13.57)	4.05 (7.99)	NS	
Subsequent Thinking Time (5 moves)	30.83 (23.45)	32.39 (20.55)	27.51(20.50)	14.78 (15.21)	NS	
Spatial Span (SSP)						
Total Errors	12.79 (5.84)	12.65 (5.27)	14.26 (5.99)	11.11 (4.7)	NS	
Total usage errors	3.25 (1.39)	1.59 (1.82)	2.64 (1.62)	1.71 (1.30)	C<H** C>M***	1.14 1.25
Mean time to 1 st response	2983.98 (478.24)	3250.23 (1191.88)	3027.10 (663.07)	3026.97 (477.44)	NS	
Mean time to last response	7350.55 (1499.08)	7114.18 (3213.55)	7776.33 (2321.40)	7927 (1778.39)	NS	
Number of attempts	8.33 (1.88)	7.69 (2.61)	8.86 (2.21)	9.46 (1.73)	C>M*	0.80
Span length	5.42 (1.02)	4.86 (1.78)	5.89 (1.29)	6.86 (1.41)	C>M**	1.17
Spatial Working Memory (SWM) (SQRT)						
Between search errors (mean)	4.81 (2.31)	4.84 (1.98)	4.10 (2.47)	3.17 (2.37)	NS	
Double search errors (mean)	0.44 (0.73)	0.62 (0.68)	0.38 (0.58)	0.31 (0.73)	NS	
Within search errors (mean)	0.56 (0.82)	0.79 (0.82)	0.52 (0.75)	0.45 (0.87)	NS	
Total errors (mean)	0.48 (2.32)	4.88 (1.99)	4.13 (2.50)	3.22 (2.37)	NS	
Strategy	5.76 (0.61)	5.37 (1.21)	5.27 (1.26)	5.15 (0.63)	NS	
Mean time to 1 st response	45.30 (7.83)	49.69 (10.85)	46.96 (9.64)	44.58 (8.51)	NS	
Mean token search preparation time	33.83 (4.47)	36.99 (4.72)	35.89 (6.31)	32.99 (4.72)	NS	
Mean time to last response	158.14 (15.83)	165.06 (15.72)	162.24 (21.91)	152.08 (14.22)	NS	

d= effect size, SQRT= Square Root transformation; Sig= Significance, *= $p < 0.01$, **= $p < 0.005$, *** = $p < 0.001$, NS= no significant impairment in neuropsychological outcomes with $p < 0.01$, H=HEROIN Group, P=CHRONIC PAIN Group, M= METHADONE Group, C=HEALTHY CONTROL Group.

Cognitive impulsivity

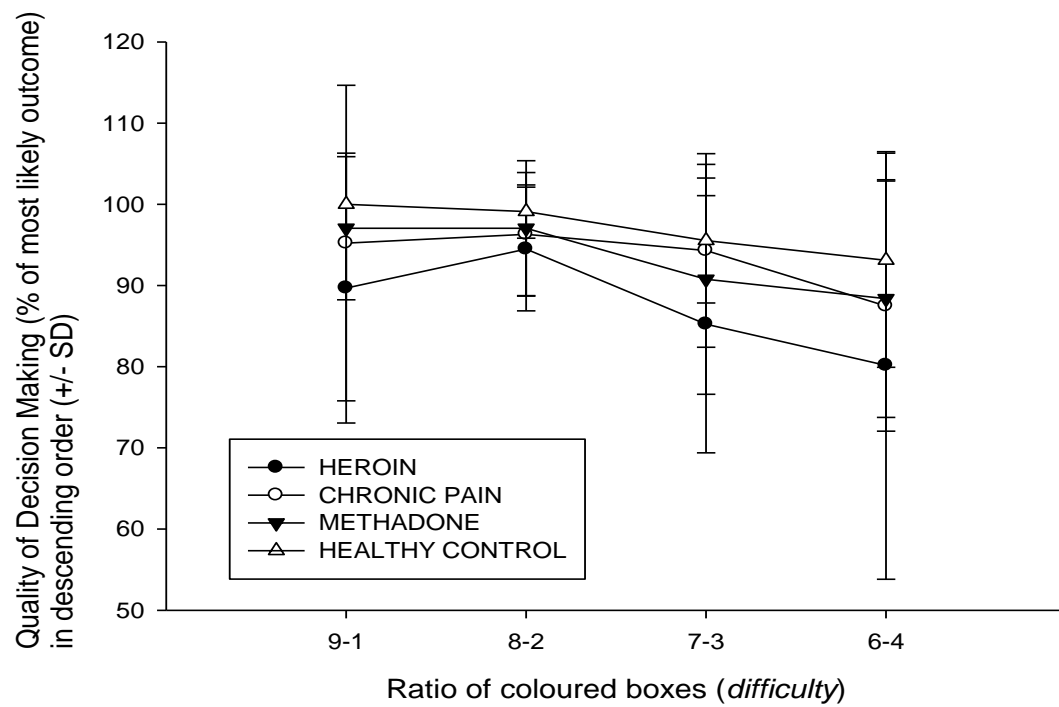
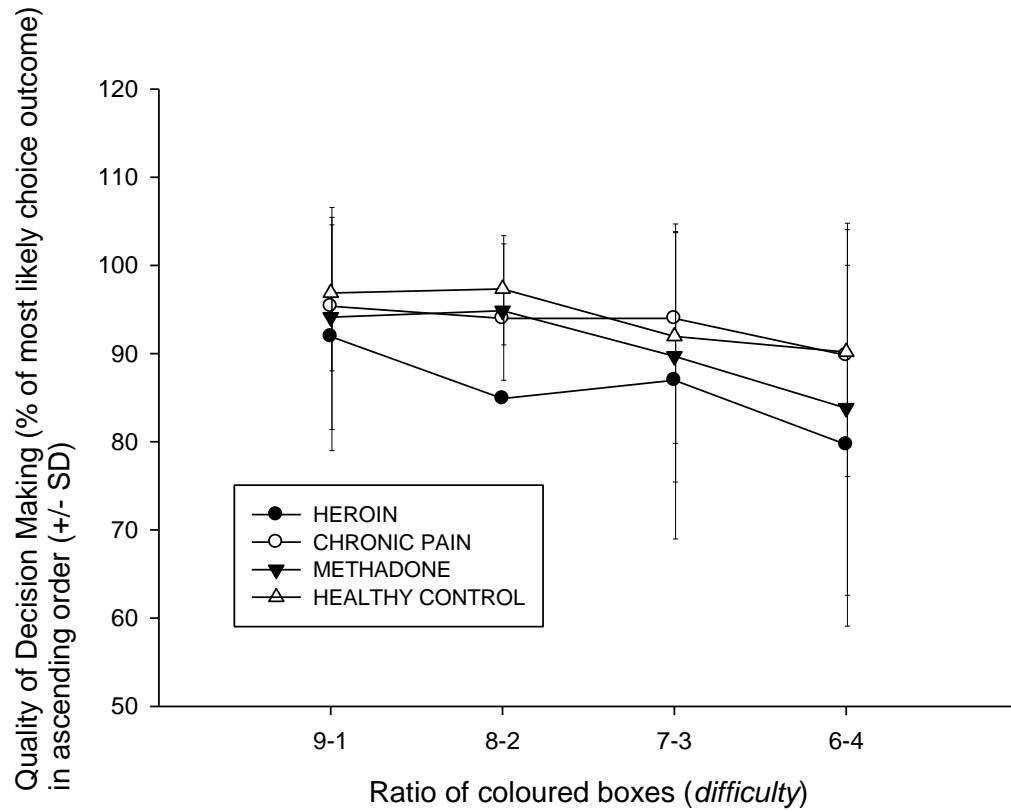
- Cambridge Gambling Task (CGT)

(a) Quality of Decision Making.

Performance on the quality of decision making of the CGT was 87.5 (0.1)% for the HEROIN and 91.2 (0.1)% for the METHADONE groups compared to 93.2 (0.19)% for the CHRONIC PAIN group and 95.5 (0.1)% for the HEALTHY CONTROL group. Participants simply won or lost the amount of points they chose to bet on each trial. Consistently choosing the least likely outcome in this task indicates poor quality of decision-making. A quality of decision making score of 89.7% for the CGT (**Rogers et al., 1999**) is usually suggested as a cut off score to reflect poor quality of decision making in substance misusers.

There was a non-significant trend for performance to be affected by GROUP [$F(3,102)=3.3, p=.02$]. Pairwise *post hoc Bonferroni* comparison showed a non-significant trend of HEROIN group ($p=.05$) and with no difference in quality of decision making between HEALTHY CONTROL, METHADONE and CHRONIC PAIN groups ($p=1.00$). There were no significant interactions [$F(9.249.72)=1.0, p=.44$] (**Figures 4.1a & 4.1b**).

There were no significant DEPENDENCE effects [$F(1,103) = 2.8, p=.09$] or INJECTING effects [$F<1$] on the quality of decision making. There were also no significant interactions [$F<1$].



Figures 4.1a & 4.1b: CGT-Quality of decision making (descending and ascending orders). Across the four difficulty levels, all participants were sensitive to decreasing likelihood of the most favourable outcome in either ascending or descending order as suggested by a reduction in quality of decision making but there were no significant GROUP [$F(3,102)=3.3, p=.02$] and interaction effects [$F(9,249.72)=1.0, p=.44$]. SD= Standard Deviation.

Overall there was no detectable significant difference in the quality of decision making across the four groups with a tendency for all groups to choose the most likely outcome. There was also no effect of DEPENDENCE and INJECTING status. When the HEROIN group was tested during different *opioid receptor occupancy states* there was no effect of opioid load on the quality of decision making [$F(2,29.597)=2.0, p=.17$]. There was also no effect on decision making quality in the METHADONE group following prolonged exposure to stable doses of methadone ($p=.64$).

(b) Deliberation Times.

There was a significant GROUP [$F(3,102)=4.3, p<0.01$] effect for deliberation times (decision latencies). *Post-hoc pair wise Bonferroni* comparisons showed that participants from the METHADONE group took significantly longer to respond than did the HEALTHY CONTROL group ($p<0.01, d=0.99$) (**Figure 4.2**). The mean deliberation times for the HEROIN and CHRONIC PAIN participants lay between those for the METHADONE and HEALTHY CONTROL participants and did not differ significantly from these two groups ($p=1.00$). There were no significant GROUP by task *difficulty* and *direction* interactions [$F(9,206.28)=1.6, p=.16$] in deliberation times.

There was a significant effect of DEPENDENCE status [$F(1,104)=7.2, p<0.01, d=0.27$] on deliberation times with increased response time latencies in those with histories of opioid dependence. There was no significant interactions with *direction* [$F(1,104)=4.94, p=.03$] or task *difficulty* [$F(3,211.75)=3.1, p=.05$].

There was no significant effects [$F<1$] or interactions [$F(6,209.55)=1.7, p=.15$] with INJECTING status.

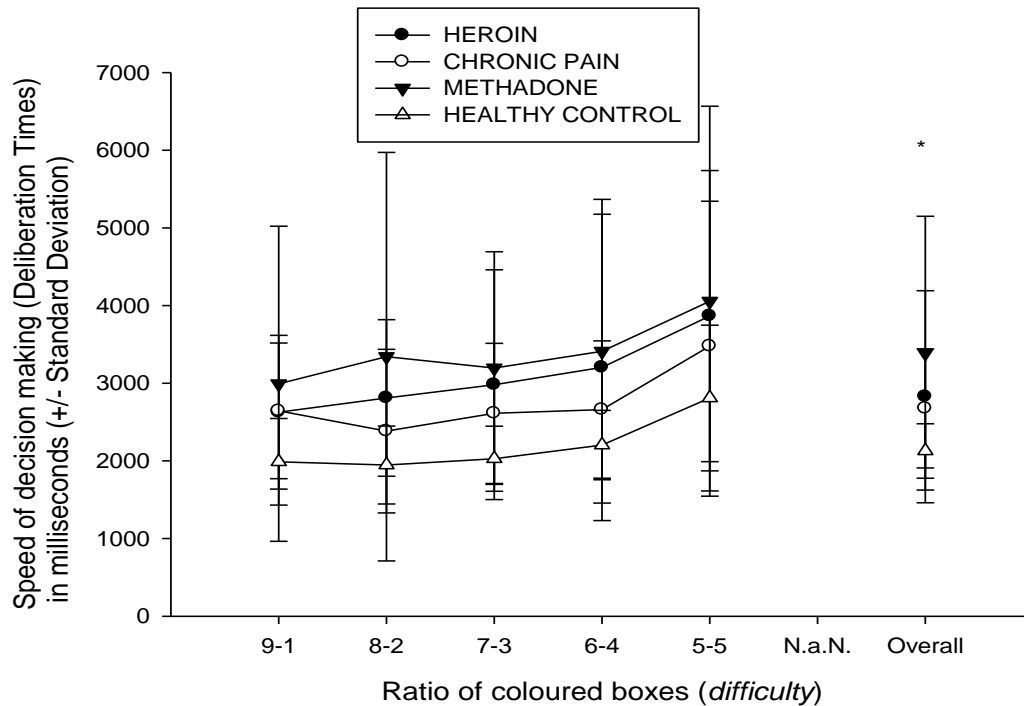


Figure 4.2: All participants were sensitive to decreasing levels of difficulty as suggested by the speed of decision making. Overall deliberation times outcomes differed significantly across the four groups [$F(3,102) = 4.3, p < 0.01$]. Participants from the METHADONE group took significantly longer to respond than did the HEALTHY CONTROL group ($*p < 0.01$). There were no significant GROUP by task difficulty and direction interactions ($p = .16$) in deliberation times.

Overall the HEROIN group was not significantly slower than any other groups. When the HEROIN group was tested during different *opioid receptor occupancy states* there was no effect on deliberation times [$F < 1$].

Overall, the METHADONE group was significantly slower in making a decision compared to the HEALTHY CONTROL group but this was not related to the difficulty levels presented or the direction of betting sequence. Since deliberation times measured the time taken for the participants to choose a colour to bet on, a longer delay is not indicative of impulsive behaviour. There was no additional effect on deliberation times in the METHADONE group following prolonged exposure to stable doses of methadone ($p = .12$).

(c) Risk Taking (Overall Proportion Bet).

There was a non-significant GROUP trend on risk taking [$F(3,101)=1.5, p=.21$].

However there was a significant GROUP by task *difficulty* and *direction* interaction [$F(9,196.89)=6.4, p<0.01$]. Overall GROUP participants placed significantly higher bets at the more favourable ratio (less *difficulty* levels) (i.e. 9:1>8.2>7.3>6:4) as shown by a significant GROUP x *difficulty* interaction [$F(9, 196.89)=6.4, p<0.001$] (**Figure 4.3**). *Post hoc Bonferroni* comparison identified the HEROIN group significantly betting more at all *difficulty* levels compared to the CHRONIC PAIN and HEALTHY CONTROL groups ($p<0.001, d=0.74$) and not significantly with the METHADONE ($p=.26$) group.

Also overall GROUP participants placed significantly higher bets in the descending order [$F(9,195.19)=7.85, p<0.001$] with a non-significant trend in the ascending order [$F(9, 215.49)=2.35, p=.03$] as shown by a significant GROUP by *direction* interaction ($F(3,101)=3.63, p<0.01$). *Post hoc Bonferroni* comparison identified the HEROIN group performing significantly worse in the descending order than the METHADONE, CHRONIC PAIN and HEALTHY CONTROL groups ($p<0.001$) (**Figure 4.3**).

There were no significant effects of DEPENDENCE status [$F(1,103)=3.3, p=.07$] or INJECTING status [$F<1$] on risk taking. There were also no significant interactions in both DEPENDENCE status [$F(3,225.53)=1.9, p=.15$] and INJECTING status [$F<1$].

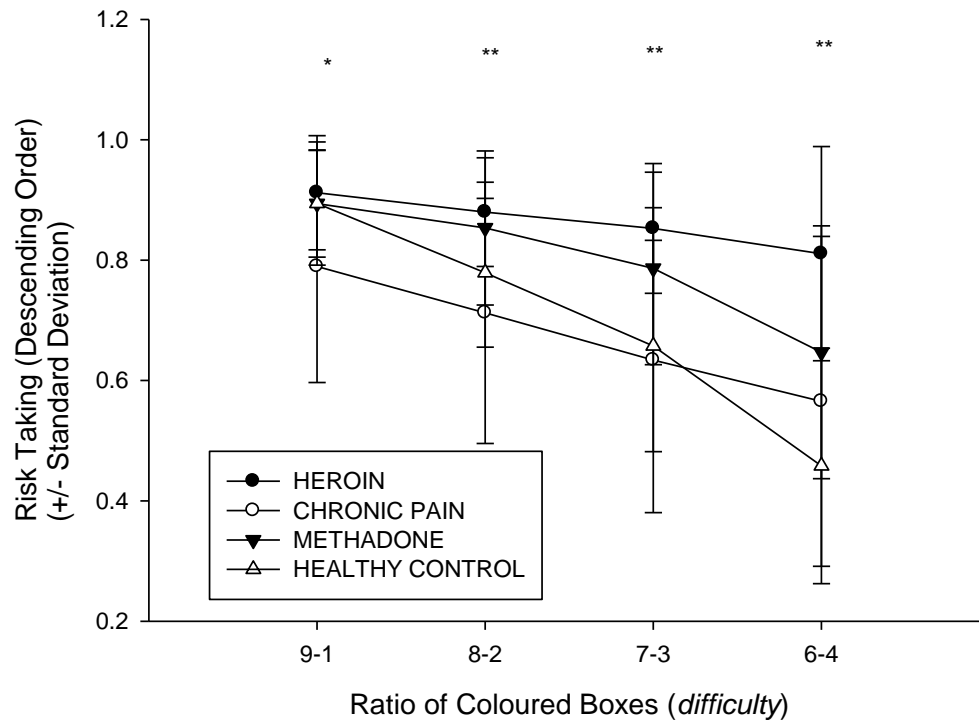


Figure 4.3: CGT-Risk Taking. Across the four difficulty levels, all participants were significantly placing larger bets at the more favourable ratio (i.e. 9:1>6:4). Overall GROUP participants placed significantly higher bets in the descending order [$F(9,195.19) = 7.85$, $p < 0.001$]. *Post hoc Bonferroni* comparison identified the HEROIN group significantly betting more at all difficulty (but not significantly at the 9:1 ratio*) levels compared to the HEALTHY CONTROL and CHRONIC PAIN (** $p < 0.001$) and not significantly with the METHADONE ($p = .26$) group.

Overall the HEROIN group significantly placed higher and earlier bets on favourable, ratios especially in the descending order compared to the HEALTHY CONTROL and CHRONIC PAIN groups but not the METHADONE group. When the HEROIN group was tested during different *opioid receptor occupancy states* there was no additional effect of opioid load on risk taking [$F(2,46) = 1.0, p = .37$]. The METHADONE group placed higher bets on favourable ratios and there was no effect on risk taking in the METHADONE group following prolonged exposure to stable doses of methadone ($p = .42$).

(d) Delay Aversion.

There was a non-significant trend for delay aversion scores by GROUP [$F(3,101) = 3.3$, $p = 0.02$].

However there was a significant GROUP by task *difficulty* and *direction* interaction [$F(9,222.23)=2.6, p<0.01$]. *Post hoc Bonferroni* comparison showed the HEROIN group was significantly unwilling to wait when 8:2, 7:3, and 6:4 ratio of coloured boxes were presented compared to the HEALTHY CONTROL ($p<0.01$), CHRONIC PAIN ($p=.03$) and METHADONE ($p<0.01$) groups and especially presented in a descending order compared to the HEALTHY CONTROL, CHRONIC PAIN and METHADONE groups ($p<0.001$) (Figures 4.4).

There were no significant effects of DEPENDENCE status [$F(1,103)= 2.9, p=.09$] or INJECTING status [$F<1$] on delay aversion. There were also no significant interactions in these two groups.

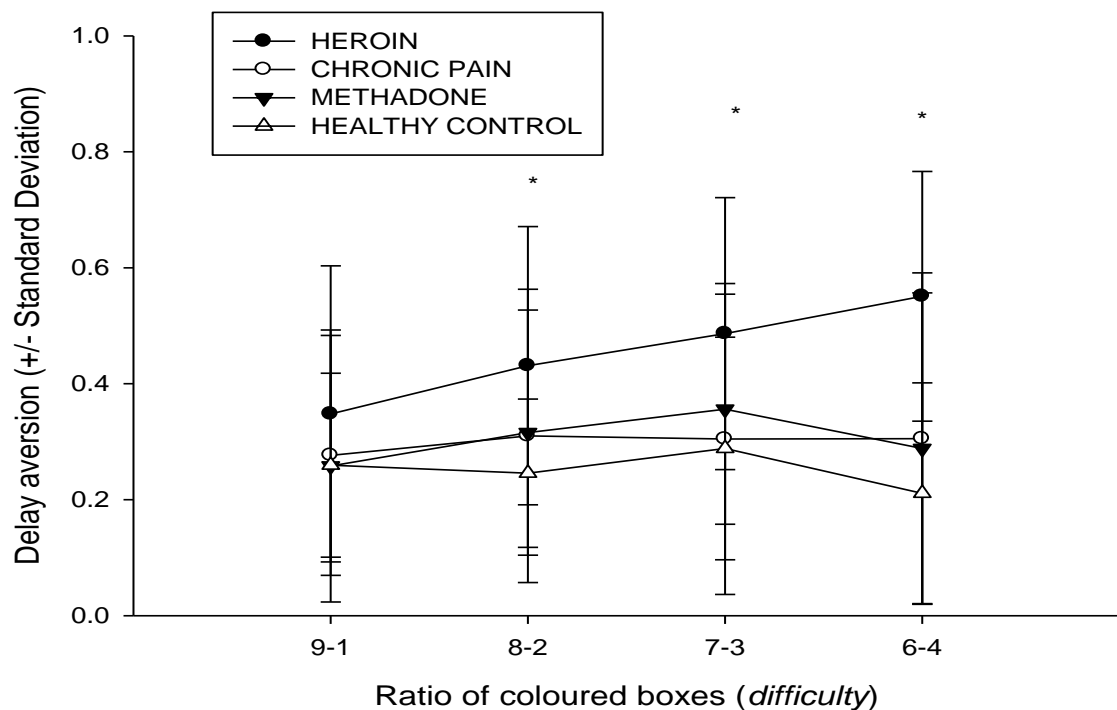


Figure 4.4: CGT-Delay Aversion. There was a significant GROUP by task *difficulty* and *direction* interaction [$F(9,222.23)=2.6, p<0.01$] with the HEROIN group exhibited impaired delay aversion compared to the HEALTHY CONTROL, CHRONIC PAIN and METHADONE groups (** $p<0.001$).

Overall the HEROIN group was unwilling to wait and resulted in betting larger amounts when the possible bet amount was presented in a descending order than when the amounts are presented in the ascending order. When the HEROIN group was tested during different *opioid receptor occupancy states*, there was no effect of opioid load on delay aversion [$F < 1$].

There was no effect on risk aversion in the METHADONE group following prolonged exposure to stable doses of methadone.

(e) Risk Adjustment.

There was a significant GROUP [$F(3,102) = 6.2, p < 0.001$] effect for overall risk adjustment. *Post-hoc pair wise Bonferroni* comparisons showed the HEROIN ($p < 0.001, d = 1.36$) and METHADONE ($p < 0.001, d = 0.94$) groups significantly increasing the percentage of available points put at risk in response to more favourable coloured box ratios compared to the HEALTHY CONTROL group (**Figure 4.5**). The CHRONIC PAIN group showed a non-significant trend for CHRONIC PAIN ($p = 0.01$) compared to HEALTHY CONTROL group.

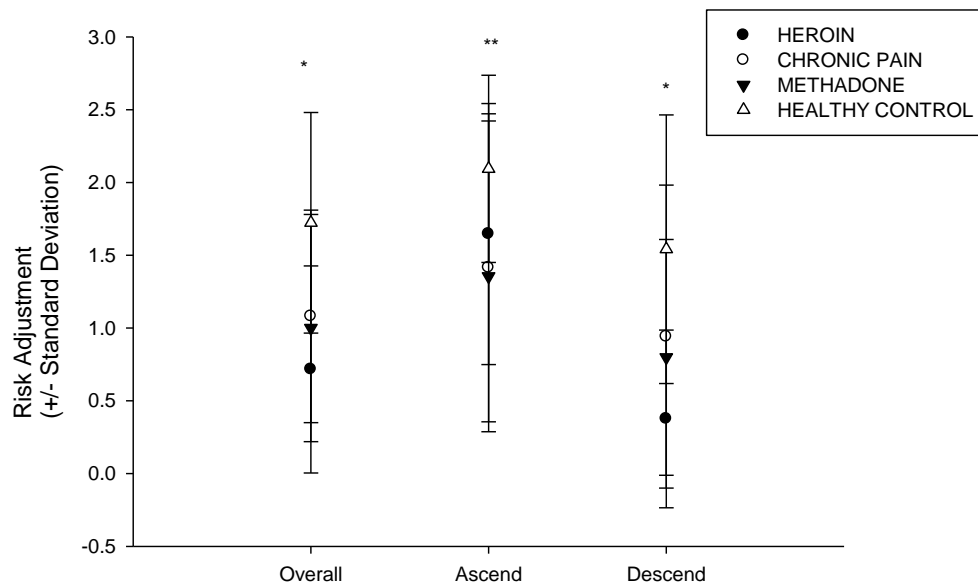


Figure 4.5: CGT -Risk Adjustment. There was a significant GROUP (** $p < 0.001$) effect for overall Risk Adjustment. There was also a significant GROUP by task *direction* interactions in both ascending (* $p < 0.01$) and descending (** $p < 0.001$) orders.

There was also a significant GROUP by task *direction* interaction in both ascending [$F(3,102)=4.4, p<0.01$] and descending [$F(3,102)=6.4, p<0.001$] orders. *Post hoc Bonferroni* comparison showed the METHADONE group significantly increased the percentage of available points put at risk in response to more favourable coloured box ratios in the ascending order compared to the HEALTHY CONTROL group ($p<0.005$) but not to HEROIN and CHRONIC PAIN groups ($p=1.00$). Meanwhile the HEROIN ($p<0.001$) and METHADONE ($p<0.01$) group significantly increased the percentage of available points put at risk in response to more favourable coloured box ratios in the descending order compared to the HEALTHY CONTROL group but not to the CHRONIC PAIN groups ($p=1.00$).

There was a significant effect of DEPENDENCE status [$F(1,104)=9.5, p<0.005$] but no effect of INJECTING status [$F<1$] on risk adjustment.

Overall the HEROIN group significantly increased the percentage of available points put at risk in response to more favourable coloured box ratios in the descending order. When the HEROIN group was tested during different *opioid receptor occupancy states*, there was no effect of opioid load on delay aversion [$F<1$].

The METHADONE group significantly increased the percentage of available points put at risk in response to more favourable coloured box ratios in both ascending and descending orders. There was no effect on risk adjustment in the METHADONE group following prolonged exposure to stable doses of methadone ($p=.42$). **Table 4.4** summarises all results from the Cambridge Gambling Task (CGT).

Table 4.4: Summary of results from analysis of CGT outcomes¹. Unless specified significance is with HEALTHY CONTROL and/or CHRONIC PAIN groups.*

Cambridge Gambling Task (CGT)	HEROIN vs METHADONE vs CHRONIC PAIN vs HEALTHY CONTROL	Opioid DEPENDENCE (OD) vs Non- Opioid DEPENDENCE (Non OD)	INJECTING vs non-injecting
Quality of Decision Making	↔	↔	↔
Deliberation time	↓ METHADONE	↓ OD > Non-OD	↔
Risk Taking	↓ HEROIN	↔	↔
Delay Aversion	↓ HEROIN	↔	↔
Risk Adjustment	↓ METHADONE & HEROIN	↔	↔

*= significant effects with $p < 0.01$, ↓=significant neuropsychological deficits present, ↔= no significant neuropsychological deficits present, ¹= ANCOVA 'between subject factor' of GROUP, DEPENDENCE and INJECTING analysed separately.

Motor Impulsivity

- Affective Go-NoGo (AGN)

There was a significant effect for commission errors by GROUP [$F(3,102)=5.4, p < 0.01$]. *Post hoc Bonferroni* comparisons revealed that the HEROIN group showed a significant effect of making more commission errors compared to the HEALTHY CONTROL group ($p < 0.00, d=1.10$) and a non-significant trend to the CHRONIC PAIN ($p=.06$) group. The METHADONE group did not differ significantly from the HEROIN, CHRONIC PAIN and HEALTHY CONTROL groups ($p=1.0$).

Further analysis indicated significant GROUP effects on commission errors when responding to happy words during sad word blocks (negative valence) [$F(3,102)=6.5, p < 0.001$] with the HEROIN group significantly ($p < 0.001, d=1.23$) and the METHADONE group showing a non-significant trend ($p=.02$) compared to the HEALTHY CONTROL group. There was also a significant GROUP effect [$F(3,102)=7.6, p < 0.01$] on commission errors in non-shift mode (when the participant's response orientation remained the same between blocks). *Post hoc Bonferroni* analysis showed the HEROIN group significantly ($p=0.01, d=1.06$) making more commission errors in the non- shift mode when compared to HEALTHY CONTROL (**Figure 4.6**).

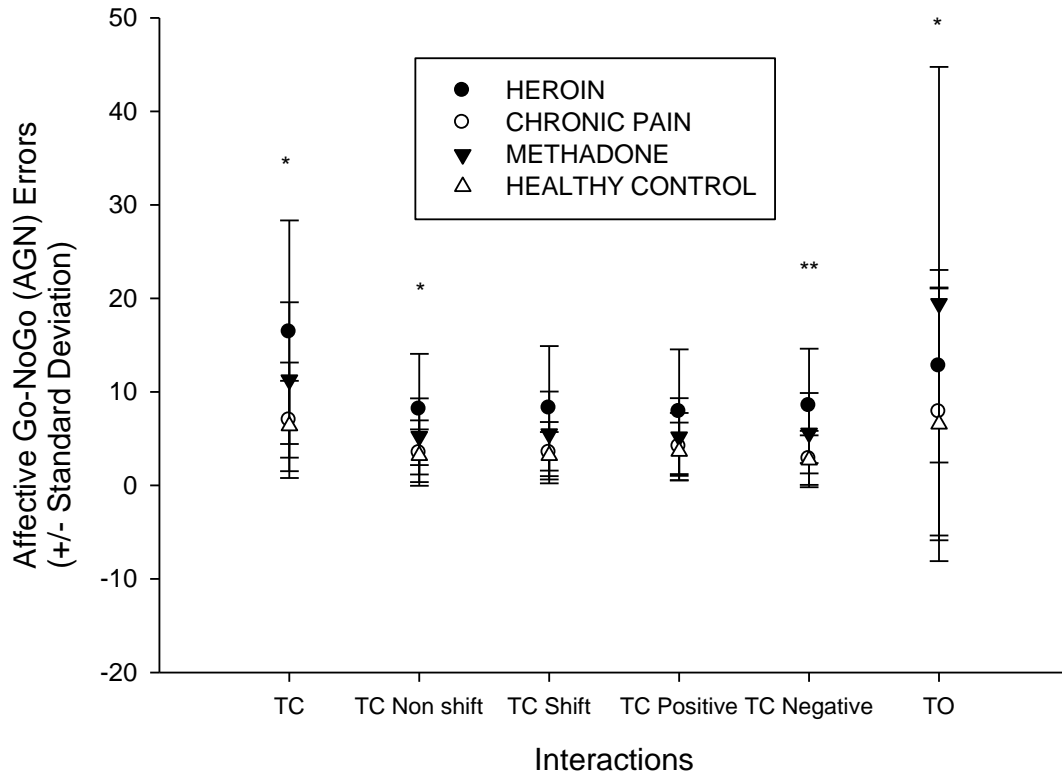


Figure 4.6: AGN-Total commission and omission errors for HEROIN, METHADONE, CHRONIC PAIN and HEALTHY CONTROL groups. There was a significant effect for commission errors [$F(3,102)=5.4, *p<0.01$], especially during negative valence ($p<0.001$) and non- shift mode ($*p<0.01$) and omission errors [$F(3,102)=4.2, p<0.01$] to be effected by GROUP.**

TC= Total Commission Errors, TO= Total Omission Errors, TC Positive=Total Commission Errors in Positive Valence, TC Negative= Total Commission Errors in Negative Valence.

There was also a significant GROUP effect [$F(3,102)=4.2, p<0.01$] on omission errors (**Figure 4.6**) but *post hoc Bonferroni* comparisons showed the METHADONE group making more omission errors when compared to the HEALTHY CONTROL ($p=.02$) and CHRONIC PAIN ($p=.02$) groups but not reaching significance. The METHADONE group did not differ significantly from the HEROIN group ($p=1.0$). There was also a non-significant GROUP trend in mean correct latency [$F<1$].

There were significant DEPENDENCE status effects on commission errors [$F(1,104)=8.9, p<0.005$], negative valence [$F(1,104)=9.4, p<0.005$] non- shift mode [$F(1,104)=6.9, p<0.01$] and omission errors [$F(1,104)=11.3, p<0.005$] but not significant to mean correct latency [$F<1$](**Figure 4.7**).

There were no significant INJECTING status effects on commission errors [$F(1,48)=2.2, p=.14$], omissions errors [$F<1$] and mean correct latency [$F(1,40)=2.8, p=.11$].

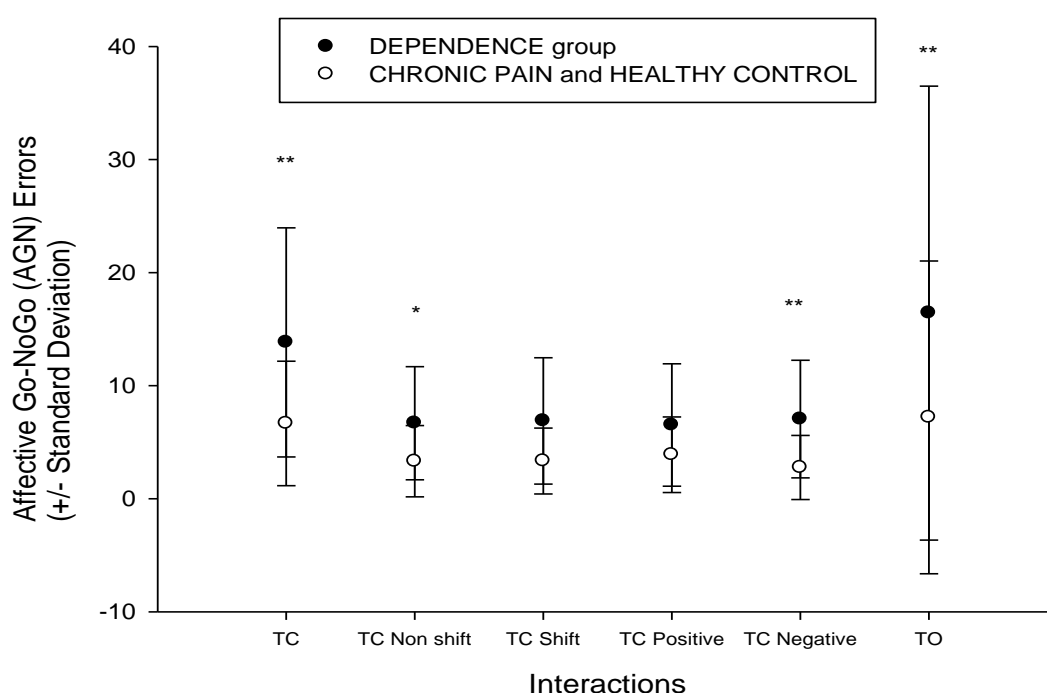


Figure 4.7: AGN-Total commission and omission errors of DEPENDENCE group compared with PAIN and HEALTHY CONTROL (non-opioid dependent) groups. There were significant DEPENDENCE status effects on commission errors [$F(1,104)=8.9, **p<0.005$] especially during negative valence [$**p<0.005$] and non- shift mode [$*p<0.01$] and on omission errors [$**p<0.005$] to be effected by GROUP. TC= Total Commission Errors, TO= Total Omission Errors, TC Positive=Total Commission Errors in Positive Valence, TC Negative= Total Commission Errors in Negative Valence.

Overall there were detectable differences in commission errors in the HEROIN group at baseline testing indicating behavioural inhibition. When the HEROIN group was tested during different *opioid receptor occupancy states* there was a significant effect

of opioid load on commission errors [$F(2,46)=6.1, p<0.001$] with *post hoc Bonferroni* analysis showing the stable methadone stage for the HEROIN group performing significantly better than the illicit (baseline)heroin stage of the same group ($p<0.01$). There was also a non-significant trend for the methadone stage of the HEROIN group to do better compared to the withdrawal stage of the same group ($p=.04$). The above significant effect was further observed in the non- shift mode of commission error scores [$F(2,44)=7.8, p<0.001$] with a non-significant trend in the shift mode [$F(2,44)=3.6, p=.03$].

The HEROIN group as well showed similarity in outcome scores with the METHADONE group in omission error scores but showing no significant effects when compared with both PAIN and HEALTHY CONTROL groups. Nevertheless inattention resulting in omission errors was present in the HEROIN group at baseline testing which did not change with different *opioid receptor occupancy states* [$F(2,29.869)=1.9, p=.17$].

The METHADONE group, however, showed non-significant inattention during baseline testing. There was no effect on commission ($p=.02$) and omission errors ($p=.12$).

Table 4.5: Summary of results from analysis of AGN outcomes¹. Unless specified significance is with HEALTHY CONTROL and/or CHRONIC PAIN groups*.

Affective Go-NoGo (AGN)	HEROIN vs METHADONE vs CHRONIC PAIN vs HEALTHY CONTROL	Opioid DEPENDENCE (OD) vs Non- Opioid DEPENDENCE (Non- OD)	INJECTING vs non-injecting
Total Commissions	↓ HEROIN	↓OD > Non- OD	↔
Total Omissions	↔	↓OD > Non-OD	↔
Mean Correct latency	↔	↔	↔

*= significant effects with $p<0.01$, ↓=significant neuropsychological deficits present, ↔= no significant neuropsychological deficits present, ¹= ANCOVA 'between subject factor' of GROUP, DEPENDENCE and INJECTING analysed separately.

Non-planning impulsivity

- Stocking of Cambridge (SOC)

There was a non-significant GROUP [$F(3,101) = 2.2, p = .09$] trend for the problems solved on minimum number of moves, subsequent thinking time [$F(3,101) = 2.2, p = .09$] and mean initial thinking time [$F(3,101) = 2.7, p = .06$].

There was a non-significant trend of GROUP by *difficulty* [$F(9,250.8) = 2.3, p = .03$] interaction for the problems solved in minimum number of moves. ANCOVA at each of the 2,3,4 and 5 move problem stages showed a significant GROUP effect at the 5-move stage [$F(3,107) = 6.0, p < 0.001$]. *Post hoc Bonferroni* comparison at the 5-move stage problem showed that participants from the HEROIN ($p < 0.01, d = 0.80$) and METHADONE ($p < 0.001, d = 0.87$) groups significantly making more moves when compared to the HEALTHY CONTROL group. Participants from the CHRONIC PAIN ($p = 0.02$) group showed a non-significant trend in making more moves when compared to the HEALTHY CONTROL group (**Figure 4.8**).

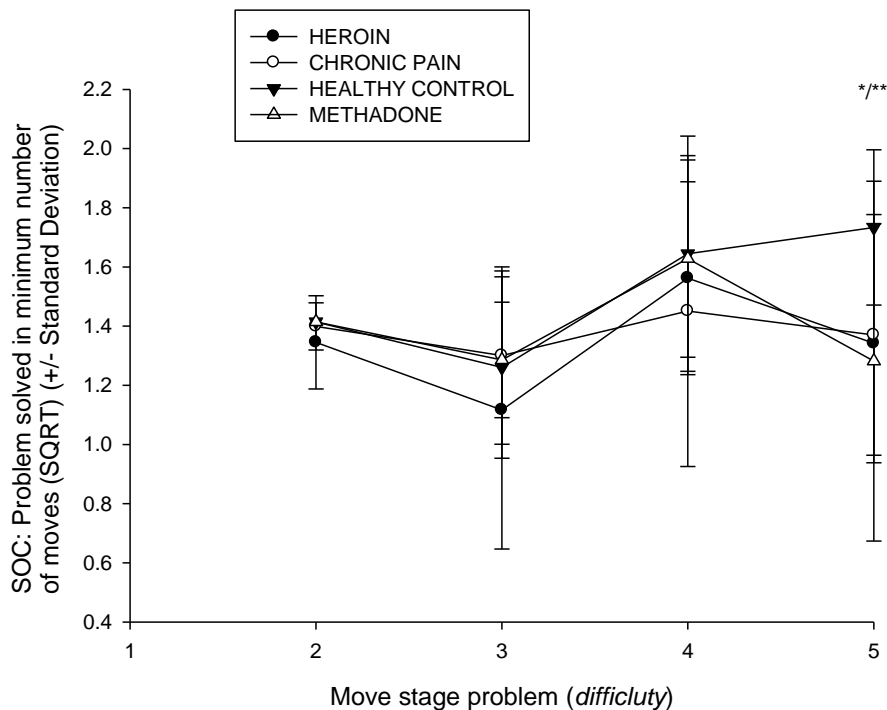


Figure 4.8: SOC and problems solved in minimum number of moves. *Post hoc Bonferroni* comparison at the 5-move stage problem showed that participants from the HEROIN ($*p < 0.01$) and METHADONE ($**p < 0.001$) groups significantly making more moves when compared to the HEALTHY CONTROL group. Participants from the CHRONIC PAIN ($p = 0.02$) group showed a non-significant trend.

There was no significant GROUP by *difficulty* interaction for: mean initial thinking time [$F(9,273.8)=2.1, p=.04$] and subsequent thinking time [$F(9,253.7)=2.4, p=.02$]. Specifically an ANCOVA at each of the 2,3,4 and 5 move problem stages revealed non-significant trends at the 2 move [$F(3,107)=3.9, p=0.01$], and 3-move [$F(3,107)=3.9, p=.01$] stages, and a significant effect at the 5-move problem [$F(3,107)=4.4, p<0.01$] stage in subsequent thinking time. *Post hoc Bonferroni* comparison showed the HEROIN group had a significant longer subsequent thinking time at the 5 move stage problem ($p<0.005$) when compared to the HEALTHY CONTROL group.

There were no significant effect of DEPENDENCE status for: problems solved in minimum number of moves [$F(1,103)=1.6, p=.21$], mean initial thinking time [$F(1,103)=2.3, p=.14$] and subsequent thinking time [$F<1$]. There were no significant interaction for: problems solved in minimum number of moves [$F<1$], mean initial thinking time [$F(3,277.22)=3.1, p=.03$] and on subsequent thinking time [$F(3,256.43)=2.8, p=.05$].

There was no significant INJECTING status effects for: problems solved in minimum number of moves [$F(1,48)=1.9, p=.17$], mean initial thinking time [$F<1$] and subsequent thinking time [$F<1$]. However there was a significant interaction with INJECTING status and *difficulty* [$F(6,260.49)=4.8, p<0.001$] for subsequent thinking time. *Post hoc Bonferroni* comparisons show that INJECTING status was significant ($p<0.01$) at the 2 stage move problem compared to the non-injecting group. There were no significant interactions with INJECTING status for: problems solved in minimum number of moves [$F<1$] and mean initial thinking time [$F(6,270.64)=1.7, p=.13$].

Overall the HEROIN group at baseline significantly struggled to solve complex problems in the minimum number of moves and took longer to solve it. Therefore the deficit is not due to motor impulsivity. When the HEROIN group was tested during different *opioid receptor occupancy states* there was no effect of opioid load on the

minimum number of moves [$F < 1$], mean initial thinking time [$F(2, 27.206) = 3.6$, $p = .06$], and subsequent thinking time [$F(2, 40) = 1.9$, $p = .16$].

The METHADONE group also had significantly less occasions upon which the participants had successfully solve a 5 move problem in the minimum number of moves. This was not complemented with more time needed to initiate or continue the task. There was no effect on the minimum number of moves needed to solve the problem task in the METHADONE group following prolonged exposure to stable doses of methadone.

Table 4.6: Summary of results from analysis of SOC outcomes¹. Unless specified significance is with HEALTHY CONTROL and/or CHRONIC PAIN groups*.

Stockings of Cambridge (SOC)	HEROIN vs METHADONE vs CHRONIC PAIN vs HEALTHY CONTROL	Opioid DEPENDENCE (OD) vs Non- Opioid DEPENDENCE (Non- OD)	INJECTING vs non- injecting
Number of problems solved in minimal number of moves.	↓ HEROIN & METHADONE at 5 move stage problem.	↔	↔
Initial thinking time	↔	↔	↔
Subsequent thinking time	↓ HEROIN at 5 move stage problem	↔	↔

*= significant effects with $p < 0.01$, ↓=significant neuropsychological deficits present, ↔= no significant neuropsychological deficits present, ¹= ANCOVA 'between subject factor' of GROUP, DEPENDENCE and INJECTING analysed separately.

- Spatial Span Task

There was a significant GROUP [$F(3, 102) = 16.8$, $p < 0.001$] effect for total usage error. *Post hoc Bonferroni* comparison showed that the participants from the HEROIN group significantly made more errors compared to the METHADONE ($p < 0.001$, $d = 1.25$) and HEALTHY CONTROL ($p < 0.005$, $d = 1.14$) groups (**Figure 4.9**). The total usage errors for the CHRONIC PAIN participants lay between those of the HEROIN, METHADONE and HEALTHY CONTROL participants and did not differ significantly from these three groups ($p = 1.0$).

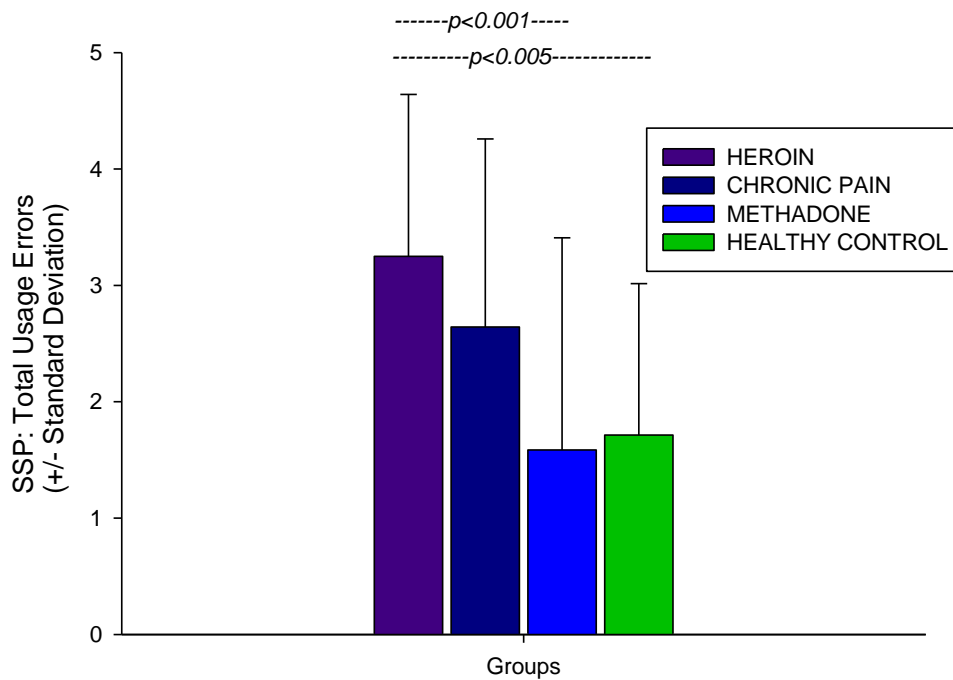


Figure 4:9: Total usage errors in Spatial Span (SSP) Task. There was a significant GROUP [$F(3,102)=16.8, p<0.001$] effect for Total Usage Error. HEROIN group participants significantly made more errors compared to the METHADONE ($p<0.001$) and HEALTHY CONTROL ($p<0.005$) groups.

There was also a significant GROUP [$F(3,101)=3.7, p<0.01$] effect for span length with *post hoc Bonferroni* comparison showing the METHADONE group significantly unable to recall successfully the longest sequence compared to HEALTHY CONTROL group ($p<0.01, d=1.17$). The span length for the HEROIN ($p=.41$) and the CHRONIC PAIN ($p=.21$) groups lay between those of the METHADONE and HEALTHY CONTROL groups and did not differ significantly from any of the other groups (**Figure 4.10**).

There were no significant GROUP effects for: the number of attempts [$F(3,102)=1.6, p=.18$], mean time to first response [$F<1$] and mean time to last response [$F<1$].

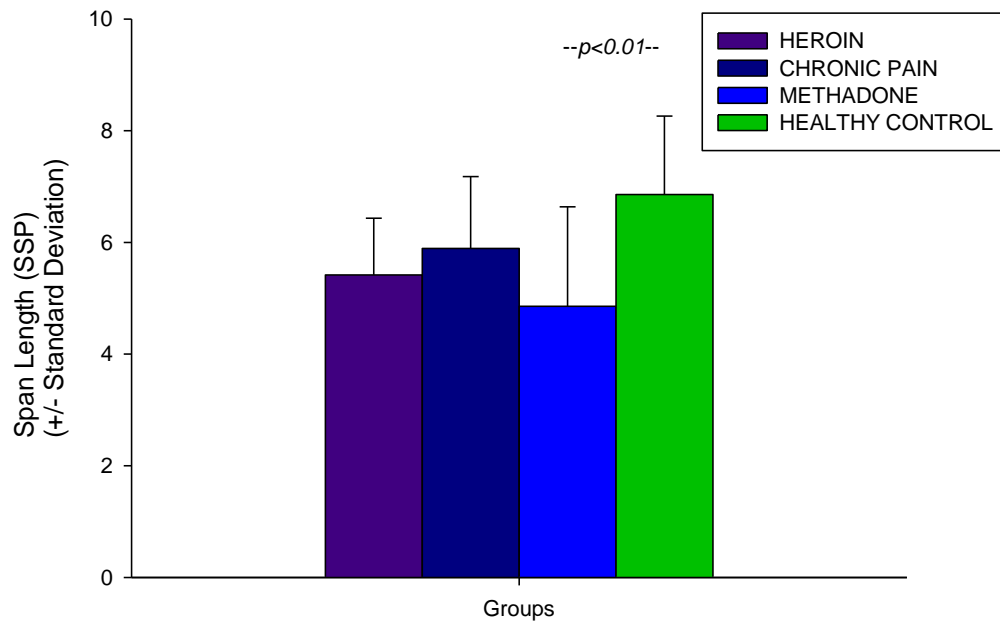


Figure 4.10: Span length in the SSP Task. There was significant GROUP [$F(3,101)=3.7, p<0.01$] effect for span length with the METHADONE group significantly unable to recall successfully the longest sequence compared to HEALTHY CONTROL group ($p<0.01$).

There was a significant effect of DEPENDENCE status [$F(1,103) = 7.1, p<0.01$] for span length (**Figure 4.11**) but no significant effect of DEPENDENCE status for: mean time to first response [$F<1$], mean time to last response [$F<1$], number of attempts [$F(1,104)=3.7, p=.06$] and total usage errors [$F(1,104)=1.1, p=.29$] of the SSP task.

There was no significant effect of INJECTING status for: span length [$F(1,47)=1.1, p=.29$], total usage errors [$F(1,48)=12.7, p=.06$], mean time to first response [$F(1,48)=8.7, p=.35$] mean time to last response [$F<1$] and number of attempts [$F<1$].

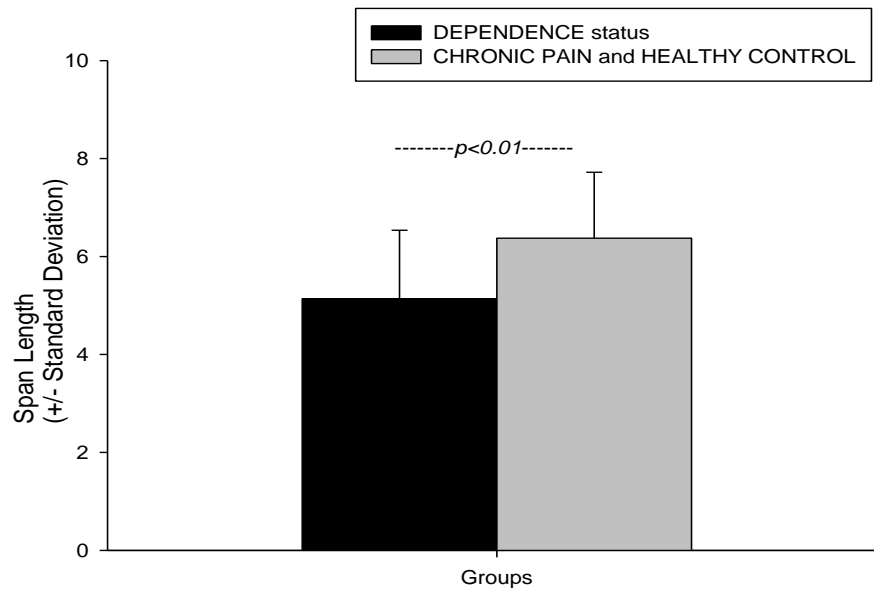


Figure 4.11: Span Length for DEPENDENCE status compared with CHRONIC PAIN and HEALTHY CONTROL groups. There was a significant effect of DEPENDENCE status [F (1,103) = 7.1, $p < 0.01$] for span length.

Overall the participants in the HEROIN group significantly selected a box not in the sequence being recalled (total usage error) when compared with the HEALTHY CONTROL participants. When the HEROIN group was tested during different *opioid receptor occupancy states* there was no effect of opioid load on all SSP outcomes (total errors [F<1], total usage errors [F (2,40)=3.4, $p = .05$], number of attempts [F<1], mean time to first response [F<1], mean time to last response [F(2,40)=2.8, $p = .07$] and span length [F<1]).

Overall participants in the METHADONE group significantly struggled to recall the longest sequence presented compared with the HEALTHY CONTROL participants. There was no effect on all spatial span outcomes in the METHADONE group following prolonged exposure to stable doses of methadone.

Table 4.7: Summary of results from analysis of SSP outcomes¹. Unless specified significance is with HEALTHY CONTROL and/or CHRONIC PAIN groups.*

Spatial Span (SSP)	HEROIN vs METHADONE vs CHRONIC PAIN vs HEALTHY CONTROL	Opioid DEPENDENCE (OD) vs Non- Opioid DEPENDENCE (Non- OD)	INJECTING vs non- injecting
Total Errors	↔	↔	↔
Total Usage Errors	↓HEROIN (also H>M)	↔	↔
Number of Attempts	↔	↔	↔
Span Length	↓METHADONE	↓OD > Non- OD	↔
Mean Time to 1 st Response	↔	↔	↔
Mean Time to Last Response	↔	↔	↔

*= significant effects with $p < 0.01$, ↓=significant neuropsychological deficits present, ↔= no significant neuropsychological deficits present, ¹= ANCOVA 'between subject factor' of GROUP, DEPENDENCE and INJECTING analysed separately. H= HEROIN group, M= METHADONE group, C= HEALTHY CONTROL group.

- Spatial Working Memory

There was a no significant GROUP effect for: total errors [$F(3,102)=3.2, p=.03$], between search errors [$F(3,100)=2.92, p=.04$], mean token-search preparation time [$F(3,100)=3.8, p=.01$], strategy score [$F(3,102)=2.9, p=.04$] and mean time to last response [$F(3,100)=3.5, p=.02$], double search errors [$F(3,102)=1.3, p=.29$], within search errors [$F(3,102)=1.5, p=.22$], and mean time to first response [$F(3,100)=2.3, p=.08$].

There was no significant GROUP and task *difficulty* interaction for the number of total errors [$F(9,130.45)=2.6, p=.04$].

There were significant DEPENDENCE effects for between search errors [$F(1,102)=6.7, p < 0.01$] and total errors [$F(3,104)=6.5, p < 0.01$], but there were no significant DEPENDENCE effects for: mean token-search preparation time [$F(1,102)=4.0, p=.05$], strategy score [$F(1,104)=4.8, p=.03$], mean time to first response [$F(1,102)=5.0, p=.03$]

and mean time to last response [$F(1,102)=3.9, p=.05$], double search errors [$F<1$] and within search errors [$F<1$].

There was a significant DEPENDENCE status and task *difficulty* interaction for total errors [$F(3,133.75)=6.2, p<0.01$] and a non-significant trend for between search errors [$F(3,181.14)=4.3, p=.02$].

There was no significant effects of INJECTING status for: between search errors [$F<1$], total errors [$F<1$], mean token-search preparation time [$F(1,47)=2.9, p=.10$], strategy score [$F<1$], mean time to first response [$F(1,47)=1.0, p=.31$] and mean time to last response [$F(1,47)=3.6, p=.07$], double search errors [$F<1$] and within search errors [$F(1,48)=1.3, p=.26$]. There was also no significant interactions [$F<1$] on all outcomes.

Overall the HEROIN group showed a non-significant trend of making more between search and total errors due to a poor strategy score compared to the METHADONE, CHRONIC PAIN and HEALTHY CONTROL groups. When the HEROIN group was tested during different *opioid receptor occupancy states* there was no effect of opioid load on all outcomes.

The METHADONE group again showed a non-significant trend of making more between search and total errors, longer latency measures [which includes mean time to last response ($p=.02$) and mean token-search preparation time ($p=.02$)] compared to the CHRONIC PAIN and HEALTHY CONTROL groups. There was a trend on all outcomes in the METHADONE group following prolonged exposure to stable doses of methadone.

Table 4.8: Summary of results from analysis of SWM outcomes¹. Unless specified significance is with HEALTHY CONTROL and/or CHRONIC PAIN groups.*

Spatial Working Memory (SWM)	HEROIN vs METHADONE vs CHRONIC PAIN vs HEALTHYCONTROL	Opioid DEPENDENCE (OD) vs Non- Opioid DEPENDENCE (Non- OD)	INJECTING vs non-injecting
Total Errors	↔	↓OD > Non- OD	↔
Between Search Errors	↔	↓OD > Non- OD	↔
Double Search Errors	↔	↔	↔
Within Search Errors	↔	↔	↔
Strategy Score	↔	↔	↔
Mean Time to First Response	↔	↔	↔
Mean Time to Last Response	↔	↔	↔
Mean Token Search Preparation Time	↔	↔	↔

**= significant effects with $p < 0.01$, ↓=significant neuropsychological deficits present, ↔= no significant neuropsychological deficits present, ¹= ANCOVA 'between subject factor' of GROUP, DEPENDENCE and INJECTING analysed separately.*

Discussion

Table 4.9 summarises the association between chronic opioid dependence and neuropsychological impairment in the cohorts studied. It describes specific significant deficits in cognitive and motor impulsivity and strategic planning in the opioid dependent population (HEROIN and/or METHADONE groups) when compared to the CHRONIC PAIN and HEALTHY CONTROL groups. Some of the deficits were significantly associated to the dependence status whilst others were not.

Table 4.9: Summary of outcomes of opioid using groups and neuropsychological functioning in impulsivity when compared with HEALTHY CONTROL group.*

Neuropsychological domain	Tests	HEROIN	METHADONE	CHRONIC PAIN	Opioid DEPENDENCE cohort	INJECTING cohort
Cognitive Impulsivity	CGT	Risk Taking, Risk Adjustment, Delay Aversion	Deliberation Time, Risk Adjustment	No impairment	Deliberation Time	No impairment
Motor Impulsivity	AGN	Total Commission Errors	No impairment	No impairment	Total Commissions (negative valence and non- shift modes) Errors, Omission Errors	No impairment
Non-Planning Impulsivity						
	SOC	Number of Minimum Moves , Subsequent Thinking Time (5 move problem)	Number of Minimum Moves (5 move problem)	No impairment	No impairment	No impairment
	SSP	Total Usage Errors	Span Length	No impairment	Span Length	No impairment
	SWM	No Impairment	No impairment	No impairment	Between Search Errors and Total Errors	No impairment

*= $p < 0.01$, no impairment= no difference in neuropsychological performance when compared to healthy controls, AGN= Affective Go-NoGo Task, CGT=Cambridge Gambling Task, SOC=Stockings of Cambridge, SSP= Spatial Span, SWM= Spatial Working Memory.

The ability to make decisions is a key element in human behaviour because this will influence how people behave in wider society (Hastie, 2001; Mellers *et al.*, 1998). Because decisions are usually made with a view to a favourable outcome, rewards provide the motivation to make decisions. Cognition is necessary to appraise the options and alternatives, assessing the means to achieve them and evaluate consequences involved with each choice (Ernst, 2005; Hastie, 2001). The results show that the chronic HEROIN dependent individuals tended to significantly place higher and earlier bets on favourable ratios (especially in the descending order) and bet more at all difficulty levels (favourable or not) reflecting a disadvantageous decision

making strategy and impulsive behaviour. The chronic and stable METHADONE participants were significantly slower in making a decision compared to the other groups which was independent of difficulty levels present (ratio of coloured boxes) or direction of betting sequence (ascending or descending order). The METHADONE group also had a tendency to place higher and earlier bets but, in this instance, on favourable ratios indicating unimpaired risk adjustment. This result is comparable to results obtained from studies conducted by **Ersche *et al.*, (2005a & 2006a); Rogers *et al.*, (1999)** and **Ornstein *et al.*, (2000)**. Since confounding variables such as young age (**Deakin *et al.*, 2004**), low intelligence quotient (**Fishbein *et al.*, 2005a**), and psychiatric mood states (**Jollant *et al.*, 2007**) and psychopathic personality disorder (**Vassileva *et al.*, 2007**) were all controlled in this study amongst others this observation could be said to be a result of (1) the chronic intake of either heroin and/or methadone, (2) the opioid dependence status, (3) past history of substance abuse and associated lifestyle and/or (4) vulnerability to trait impulsivity (**de Wit, 2009; Ersche *et al.*, 2010**) and its involvement in drug use experimentation, abuse and dependence and/or relapse after a period especially of abstinence (**Koob & Volkow, 2010**). In this study, no such deficits were observed in the CHRONIC PAIN population tested and the dependence and injecting status of the HEROIN and METHADONE groups did not indicate specific deficits in impulsivity excluding the possibility of (1) & (2) from the above. The deficits observed also did not change with either different opioid receptor occupancy or duration of methadone used. It is difficult from this study to determine if this is predominately due to statements (3) or (4) from the above or a combination of both. These statements should still be interpreted with caution until similar results are seen to be repeated in other independent studies.

The index of motor impulsivity or the inability to stop a planned movement is the number of false responses or commission errors on the Affective Go-NoGo task (**Chikazoa *et al.*, 2007, Konishi *et al.*, 1998**). This study clearly observed significant impairment in this outcome with the HEROIN participants who improved when stabilised on methadone after a month. There was a trend for the METHADONE

group to have the same inability to stop a planned movement but did not reach significance. Significantly the METHADONE group but not the HEROIN group (possibly due to a low statistical power) showed lack of attention as well as behavioural inhibition reflected by a higher rate of false misses (omissions).

These results are in contrast to the majority of studies which did not find behavioural inhibition deficits in opioid users (**Fishbein *et al.*, 2007; Rounsaville *et al.*, 1982; Passetti *et al.*, 2008; Verdejo-Garcia *et al.*, 2007a; Vainio *et al.*, 1995**) but in agreement with **Fillmore & Vogel-Sprott (1999); McNairy *et al.*, 1984** and **Forman *et al.* (2004)** who compared opioid-dependent individuals with healthy controls on the Go-NoGo task. Their findings significantly showed poorer performance in opioid dependent individuals.

Again there were no significant impairments recorded from the CHRONIC PAIN group in our study. The deficits seen in the HEROIN and less so in the METHADONE group could again be indicative of vulnerability traits but equally the HEROIN group showed signs of improvement when the cohort was stabilised on methadone. This improvement was not observed in the METHADONE group after the extended stabilisation period. Opioid dependence was a significant variable but injecting status was not. The results indicate a deficit in motor impulsivity in the HEROIN dependent participants independent of the amount of opioid used or method of administration as observed in **Rogers *et al.* (1999a)** and **Clark *et al.* (2006)**.

The ability to think ahead and actively search for an appropriate solution (non-planning impulsivity) is essential in many daily activities (**Owen, 1997**). There were significant differences between groups in performance to either first or subsequent and more complex stages of the Stocking of Cambridge (SOC) which required differential planning ability. Similar to the results in this cohort, the SOC or equivalent task in previous studies showed impairment in opioid dependent individuals (**Ornstein *et al.*, 2000; Ersche *et al.*, 2006a**).

In addition performance on tasks requiring complex spatial executive memory function and visuo-spatial strategy generation were impaired in this cohort as described in previous studies by **Ornstein *et al.* (2000)** and **Ersche *et al.* (2006a)**. The METHADONE group struggled most to recall longer sequences presented (span length) in the SSP task indicating memory deficits. HEROIN participants had significant impaired planning problems especially when a high level of difficulty was presented. This is comparable with previous studies (**Ersche *et al.*, 2006a; Shallice, 1982; Owen *et al.*, 1990**).

Opioid addiction involved neuroadaptive changes within large-scale striato-thalamo-orbitofrontal networks implicated in the processing of natural rewards and the regulation of behaviour (**Everitt & Robbins, 2005**). These changes cause the overvaluing of drug reinforcers at the expense of the undervaluing of natural reinforcers with deficits in inhibitory control of drug responses (**Goldstein & Volkow, 2002**). As a result, impaired behavioural control at the level of the prefrontal cortex is widely believed to be crucial to the addiction process (**Koob & Volkow, 2010; Everitt & Robbins, 2005; Dawe *et al.*, 2004**). More specifically neuroanatomical models suggest the existence of separate but interconnecting 'impulsive' and 'compulsive' cortico-striatal circuits (**Brewer & Potenza, 2008**). In the impulsive circuit, a striatal component (ventral striatum/nucleus accumbens shell) driving impulsive behaviours and a prefrontal component (anterior cingulate cortex, ventromedial prefrontal cortex (VMPFC) and orbitofrontal cortex (OFC)) exerting the inhibitory control (**Fineberg *et al.*, 2009**). Models of vulnerability to opioid dependence are suggestive and most studies originate from what are essentially predominantly alcohol and /or cocaine dependent studies. **Verdejo-Garcia *et al.*, (2008b)** suggest that genetic associations, especially DRD2 polymorphism, with addiction vulnerability cannot conclusively implicate trait impulsivity (**Perez de Los Cobos *et al.*, 2007; Xu *et al.*, 2004**). However there seems to be a more persuasive evidence of increased vulnerability to impulsivity in high risk children of substance use disorders parents prior to onset of their drug use (**Kendler *et al.*, 2003**) and in siblings of drug users (**Ersche *et al.*, 2010**).

Overall this study has tested the hypothesis that chronic opioid dependence was associated with neuropsychological impairment reflected in altered performance on measures of impulsivity. The HEROIN group exhibited increased cognitive and motor impulsive behaviours and associated poor strategic planning (non-planning impulsivity). The METHADONE group were slow to react, inattentive and experienced associated memory problems. The hypothesis that injecting status, the degree of acute opioid exposure (acute intoxication, withdrawal or stable initial exposure to methadone) and/or duration of opioid exposure (period of methadone maintenance) in an opioid dependent population would experience altered performance on measures of impulsivity has not been confirmed in this study. The CHRONIC PAIN group did not experience deficits in impulsivity and so the above results posit the notion that these impairments were related to trait vulnerabilities in impulsivity with a relative shift in the types of deficits from global executive dysfunction in the HEROIN group to inattention in the METHADONE group indicating neuropsychological improvement in impulsivity outcomes with methadone treatment.

Conclusion

Heroin dependence produced difficulties in strategic planning and risk taking. Motor impulsivity in HEROIN users improved once stabilised on methadone which could possibly be explained by the level of acute intoxication which might have affected the result or the actual effect of the methadone after three weeks of stabilisation. Dependence and injecting status do not contribute to the causation or deterioration of any of the identified deficits.

Chapter 5: Results-Neuropsychological functioning in men with a history of chronic opioid use: Cognitive flexibility

Background

Cognitive flexibility has been described as the ability to shift avenues of thought and action in order to perceive, process, and respond to situations in different ways (Eslinger & Grattan, 1993; Ersche *et al.*, 2010; Fineberg *et al.*, 2009). The Wisconsin Card Sorting Test (WCST) (Grant and Berg, 1948) and the Intra/Extra-Dimensional (IED) Set Shifting task of the CANTAB test battery (Downes *et al.*, 1989; Rogers *et al.*, 2000b) have been widely used to assess cognitive flexibility in opioid dependence in laboratory settings (Chapters 1 & 2 and Table 5.1).

Table 5.1: Cognitive flexibility domains.

Main Domain	Subtypes	Other names	Definition	Examples of test
Cognitive Flexibility		Cognitive Rigidity	Ability to shift avenues of thought and action in order to perceive process and respond to situations in different ways (concrete approaches to problem solving)	
	Reactive Flexibility	Perseveration or shifting of perceptual set	Ability to realign a behavioural predisposition to altered contingencies	WCST, ST, IED, TMT, SCT, MCST
	Spontaneous Flexibility or fluency	Verbal and non-verbal fluency	Requires the intrinsic generation of responses or alternatives	COWAT, FAS, VFT, RFFT, WAIS III (Similarities), RWT

COWAT= Controlled Oral Word Association Test, FAS= Phonological Fluency Test, IED= Intra/Extra-Dimensional Test (CANTAB), MCST= Maudsley Card Sorting Test, RWT= Regensburger Word Fluency Test, SCT= Logan Stop Change Task, ST= Stroop Test, TMT= Trail Making Test, VFT= Benton Verbal Fluency Test, WCST= Wisconsin Card Sorting Test, WAIS-III= Weschler Adult Intelligence Scale Third Edition.

Studies in current and former opioid users have reported contradictory findings. Studies either did not identify impairments in cognitive flexibility, suggesting that chronic opioid consumption does not have an impact on, for example, attentional set-shifting (Ersche *et al.*, 2006a; Pau *et al.*, 2002; Rotheram-Fuller *et al.*, 2004; Verdejo-

Garcia *et al.*, 2005a, 2005b; Verdejo-Garcia & Perez-Garcia, 2006); or, identified impairment in dependent heroin users (Stevens *et al.*, 2007; McNairy *et al.*, 1984), in abstinent heroin cohorts (Verdejo-Garcia *et al.*, 2007a, Brand *et al.*, 2008) and/or methadone users (Darke *et al.*, 2000; Mintzer *et al.*, 2005; Pirastu *et al.*, 2006) (Table 5.2).

Table 5.2: Chronic opioid use and cognitive flexibility. Previous research findings.*

Neuropsychological domain	Illicit chronic heroin use	Abstinent ex-heroin use	Methadone use	Other opioid use ¹	Chronic opioid dependence
Cognitive Flexibility (ability to shift attentional set)	Hill <i>et al</i> (1979)↓ Stevens <i>et al</i> (2007)↓ McNairy <i>et al</i> (1984)↔	Verdejo-Garcia <i>et al</i> (2007a)↓ Fishbein <i>et al</i> (2007)↓ Brand <i>et al</i> (2008)↓	Darke <i>et al</i> (2000)↓ Mintzer <i>et al</i> (2005)↓ Rotheram-Fuller <i>et al</i> (2004)↔ Pirastu <i>et al</i> (2006)↓ Prosser <i>et al</i> (2006)↓ Rounsaville <i>et al</i> (1982)↔ Soyka <i>et al</i> (2008)↓	Pirastu <i>et al</i> (2006)↓ Soyka <i>et al</i> (2008)↓ Jamieson <i>et al</i> (2003)↑ Tassain <i>et al</i> (2003)↔ Schindler <i>et al</i> (2004)↔	Ersche <i>et al</i> (2006)↓ Ornstein <i>et al</i> (2000)↓
Cognitive Flexibility (verbal fluency)		Prosser <i>et al</i> (2006)↔ Verdejo-Garcia <i>et al</i> (2007a)↓ Brand <i>et al</i> (2008)↔	Darke <i>et al</i> (2000)↓ Soyka <i>et al</i> (2008)↓ Prosser <i>et al</i> (2006)↔	Soyka <i>et al</i> (2008)↓	Ornstein <i>et al</i> (2000)↓

*= $p < 0.05$; ↔ = no difference in neuropsychological (compulsivity) performance; ↓ = neuropsychological (compulsivity) deficits present; ↑ = improvement in neuropsychological (compulsivity) performance when compared to healthy controls, other opioid use¹ = buprenorphine, morphine, oxycodone and tramadol.

The WCST and IED tasks both assess the capacity to relearn a stimulus-reward association by inhibition of the previously reinforced dimension (i.e. reversal shift) as observed in both animal (Dias *et al.*, 1996) and human (Rogers *et al.*, 2000a) studies. No impairments were observed in chronic opioid users on the reversal shift in the IED task (Ersche *et al.*, 2006a; Ornstein *et al.*, 2000). However impairment in reversal shift on the WCST has been described with early methadone withdrawal (Lyvers

&Yakimoff, 2003), co-morbid alcohol dependence and history of previous heroin overdoses (**Darke *et al.*, 2000**) but does not seem to be a consistent, or characteristic, behavioural correlate of opioid dependence.

In light of the previous research in the area of opioid dependent use and neuropsychological functioning, the present study set out to expand on the current limited knowledge base by comparing the neuropsychological performance of chronic heroin dependent users, methadone maintained male participants and others taking opioids for chronic pain compared to non- substance using healthy controls as explained in Chapter 3 of this thesis. This will help test the hypothesis (1):

(1) Is chronic opioid dependence associated with neuropsychological impairment reflected in altered performance on measures of compulsivity?

As previously described in Chapter 4, at least three factors were considered to be related to drug taking which may exert an important influence over neuropsychological performance. These include: (1) duration of opioid use, (2) level of opioid receptor occupancy during behavioural testing-(a) during intoxication, (b) during withdrawal and (c) during stable methadone maintenance and (3) injecting status. Therefore the next two related hypotheses (2 and 3) to be tested were:

(2) In patients with chronic opioid dependence, is injection status associated with neuropsychological impairment as reflected in altered performance on measures of compulsivity?

(3) In patients with chronic opioid dependence is the degree of acute opioid exposure (acute intoxication, withdrawal or stable initial exposure to methadone), or duration of opioid exposure (period of methadone maintenance) associated with neuropsychological impairment as reflected in altered performance on measures of compulsivity?

Statistical considerations

Basic statistical considerations have been described in Chapter 2. The data from the IED tasks violated assumptions of normality and homogeneity of variance. To stabilise variance and diminish *skewness* and *kurtosis*, IED data were subjected to square root (*SQRT*) transformation (Fields, 2009).

Testing hypotheses 1 and 2

Data from the IED were initially analysed using univariate or repeated measures ANCOVA with a *between subject factor* of GROUP (HEROIN vs. METHADONE vs. CHRONIC PAIN vs. HEALTHY CONTROL) and *difficulty* as expressed by the nine IED stages as a *within-subjects factor*. NART, age in years, SIMD, total Fagerström score, years in education and past alcohol use in years were considered as covariates.

Further *a priori* subgroup analysis for the IED was conducted using (1) a two-group factor reflecting DEPENDENCE (HEROIN and METHADONE groups vs. CHRONIC PAIN and HEALTHY CONTROL groups) and (2) a two-group factor reflecting lifetime INJECTING (HEROIN and METHADONE injecting vs. HEROIN and METHADONE never injecting groups) separately as the *between subject factors*.

Between-group effects in ANCOVA were analysed as follows. A planned *post hoc* comparison between the HEALTHY CONTROL and the three experimental groups (HEROIN, METHADONE and CHRONIC PAIN) was used to detect any difference in performance. In this four-group model, significant *between-group effects* were investigated using pair-wise comparisons with *Bonferroni* correction procedure. Effect sizes for the group comparisons were calculated using Cohen's *d*, (i.e. the difference between the means divided by the pooled standard deviation) (Cohen, 1988).

Testing hypothesis 3

Repeated measures ANCOVA was used to evaluate IED task performance between the HEROIN group participants at baseline (whilst on illicit heroin), in controlled opioid withdrawal and subsequently when stabilised on methadone according to the

tolerance testing procedure protocol with presumed *opioid receptor occupancy state* as a *within subject factor* to determine whether performance on the IED task was modified by different degrees of opioid receptor occupancy (heroin, withdrawal and stable on methadone).

Similarly repeated measures ANCOVA was also performed to follow up IED performance for the METHADONE group at baseline and at 6 months follow up with *duration* as a *within subject factor* to determine whether any aspects of performance improved or deteriorated with time and continued exposure to chronic, sustained released opioid (methadone). .

The homogeneity of variance across groups in repeated-measures design ANCOVAs was assessed by the Mauchly Sphericity Test (**Mauchly, 1940**). Where data sets significantly ($p < 0.05$) violated this requirement for a repeated-measures design ANCOVA, the Greenhouse Geisser Epsilon (ϵ) correction parameter for degrees of freedom (**Greenhouse & Geisser, 1959; Winer *et al.*, 1991**) was used to calculate a more conservative p value for each F ratio.

Results

All subjects completed all of the tests. Mean performance (not adjusted for covariates), statistical comparisons and effect sizes (d) for each task, for the HEROIN, METHADONE, CHRONIC PAIN and HEALTHY CONTROL groups, are summarised in **Table 5.3**.

Table 5.3: Summary of baseline neuropsychological findings in cognitive flexibility (not adjusted for covariates).

Compulsivity or lack of cognitive flexibility	HEROIN N= 24	METHADONE N= 29	CHRONIC PAIN N= 28	HEALTHY CONTROL N= 28		
<i>IED (SQRT)</i>						
Stages Completed	8.19 (1.91)	8.64 (1.05)	8.50 (1.20)	8.56 (0.99)	NS	
Total Errors	5.07 (1.31)	4.34 (1.41)	4.57 (1.23)	3.10 (1.12)	C<H *	1.62
Pre ED Shift Errors	2.73 (1.07)	2.48 (0.65)	2.35 (0.63)	2.32 (0.49)	NS	
ED Shift Errors	3.20 (1.76)	2.70 (1.46)	3.27 (1.51)	2.77 (1.41)	NS	

d= effect size, *SQRT*= Square Root transformation; *Sig*= Significance, * = $p < 0.01$, ** = $p < 0.005$, *** = $p < 0.001$, NS= no significant impairment in neuropsychological outcomes with $p < 0.01$, H=HEROIN Group, P=CHRONIC PAIN Group, M= METHADONE Group, C=HEALTHY CONTROL Group.

Cognitive flexibility

- **Intra/Extra-Dimensional Set Shifting (IED) Task**

All participants from the four groups succeeded in completing all nine stages of the IED task.

There was a non-significant GROUP [F (3,102) =3.9, $p=.01$] trend for total mean errors. *Post hoc Bonferroni* comparisons showed that participants from the HEROIN group had significantly made more errors on the IED tasks compared to the HEALTHY CONTROL group ($p<0.01$, $d=1.62$) (**Figure 5.1**). The total mean errors for the CHRONIC PAIN ($p=.70$) or METHADONE ($p=.16$) groups lay between those for the METHADONE and HEALTHY CONTROL groups and did not differ significantly from any of the other two groups.

However there were no significant GROUP effects for pre-EDS errors [F (3,102) =0.4, $p=.76$] and EDS error scores [F (3,102) =2.2, $p=.09$] There were no significant GROUP by task *difficulty* interactions for all IED outcomes.

There was no effect of DEPENDENCE status effects for: total errors [F (1,104) =3.4, $p=.07$], pre-EDS errors and EDS errors [$F<1$]. There was also no effect of INJECTING

status for: total errors and pre-EDS errors [$F < 1$] and EDS errors [$F(1, 48) = 4.5, p = .04$]. There was no significant DEPENDENCE or INJECTING interaction for all IED outcomes.

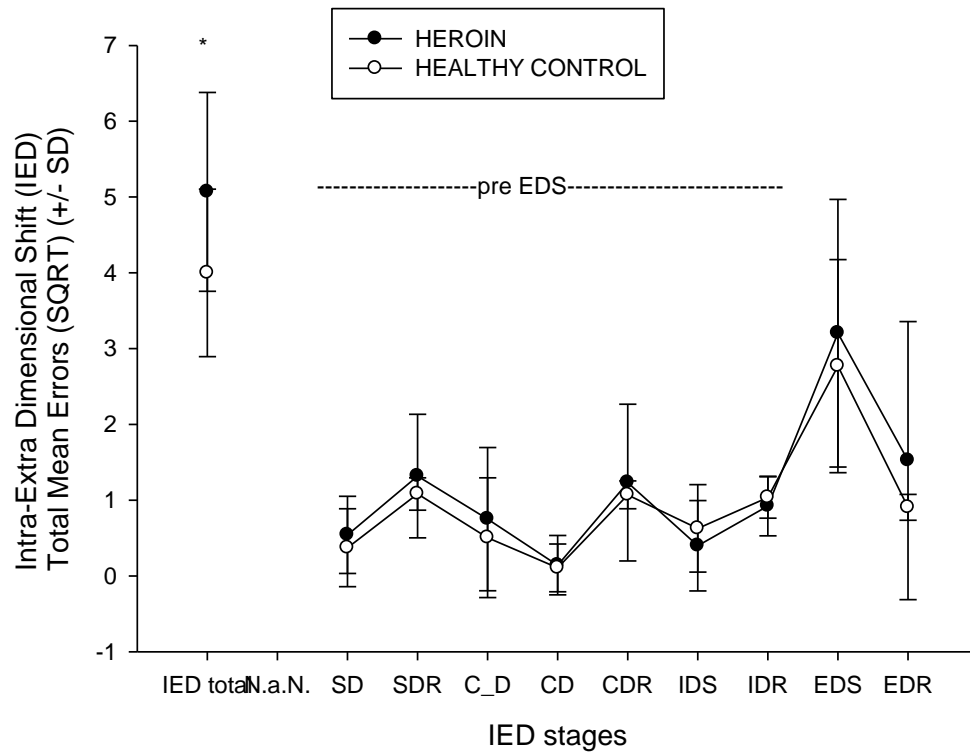


Figure 5.1: IED- Total mean errors of the HEROIN and HEALTHY CONTROL groups with the HEROIN group making significantly more errors on the total IED tasks compared to the HEALTHY CONTROL group ($*p < 0.01$). SD= Simple Discrimination, SDR=Simple Reversal, C_D= Compound Discrimination, CD=Compound Discrimination, CDR= Compound Reversal, IDS=Intra-Dimensional Shift, IDR= Intra-Dimensional Reversal, EDS= Extra-Dimensional Shift, EDR= Extra-Dimensional Reversal, pre-EDS= Pre- Extra-Dimensional Shift.

Overall participants from the HEROIN group significantly made more total errors in the IED tasks compared to the HEALTHY CONTROL group ($p < 0.01$) but not to the CHRONIC PAIN or METHADONE groups. When the HEROIN group was tested during different *opioid receptor occupancy states* there was no effect of opioid load on all the IED outcomes. There was also no effect on all IED outcomes in the METHADONE group following prolonged exposure to stable doses of methadone (**Table 5.4**).

Table 5.4: Summary of results from analysis of IED¹ outcomes. Unless specified significance is with HEALTHY CONTROL and/or CHRONIC PAIN groups*.

Intra-Extra Dimensional Shift Test (IED)	HEROIN vs METHADONE vs CHRONIC PAIN vs HEALTHY CONTROL	Opioid DEPENDENCE (OD) vs Non- Opioid DEPENDENCE (Non-OD)	INJECTING vs non- injecting
IED Stages Completed	↔	↔	↔
Total Mean Errors	↓ HEROIN	↔	↔
ID (Pred EDS) Errors	↔	↔	↔
EDS Errors	↔	↔	↔

*= significant effects with $p < 0.01$, ↓=significant neuropsychological deficits present, ↔= no significant neuropsychological deficits present, ¹= ANCOVA 'between subject factor' of GROUP, DEPENDENCE and INJECTING analysed separately.

Discussion

Table 5.5 summarises the neuropsychological outcomes of the opioid using groups with respect to cognitive flexibility. Set-shifting represents the ability to switch attention from one aspect of a stimulus to another in an ongoing task, as a result of changing reinforcement contingencies (Chapter 2).

Table 5.5: Summary of outcomes of opioid using groups and neuropsychological functioning in cognitive flexibility when compared with the HEALTHY CONTROL group*.

Neuropsychological domain	Tests	HEROIN	METHADONE	CHRONIC PAIN	Opioid DEPENDENCE	INJECTING
Cognitive Flexibility	IED	Total mean errors	No impairment	No impairment	No impairment	No impairment

*= $p < 0.01$, no impairment= no difference in neuropsychological performance when compared to healthy controls, IED= Intra/Extra-Dimensional Set Shifting Task.

The HEROIN group made significantly more errors than participants in the HEALTHY CONTROL group throughout the multiple stages of the IED task. At the pre EDS stage participants needed to maintain attention to the same dimension for correct responding, thus testing their ability to generalise the rule they had just learned (Roberts *et al.*, 1988). In normal psychologically unimpaired individuals, choice behaviour in a sensorimotor association task requires structure learning processes

and cannot be just accounted for by forming specific associations between sensory stimuli and motor responses (**Braun et al., 2010**). It is suggested that normal and unimpaired individuals learn much more than specific stimulus-response associations, namely that they also learn to extract abstract invariants that are applicable to a broad class of tasks (**Trobalon et al., 2003**). The HEROIN group showed generalisation errors with a cognitive inability to move from a learned specific rule to another possibly due to lack of attention and associated impairment in applied learning processes (**Ornstein et al, 2000**).

Set shifting impairments were not observed in any of the other experimental groups suggesting no significant impairment in cognitive flexibility. Therefore the hypothesis that chronic opioid dependence was associated with neuropsychological impairment reflected in altered performance on measures of cognitive flexibility (cognitive rigidity) has not been confirmed.

The degree of acute opioid exposure, injecting status and duration of opioid exposure did not significantly alter performance on measures of cognitive flexibility in this study. Compared to previous studies discussed earlier (Chapter 1) cognitive rigidity was evidently present during most opioid related states (heroin, methadone and/or other opioid use/abuse and abstinence from any opioids) but in most studies one could not clearly define the contribution of confounding variables present in the population studied.

In **McNairy et al., 1984**, the heroin group tested, showed significant deficits in cognitive flexibility amongst other outcomes, but this cohort were also experiencing chronic pain. The authors suggested that the neuropsychological impairment could have been caused by the chronic use of opioids and compounded by the '*slowed, disorganised or inappropriate responses to environmental demands for adaptive and stressful behaviour such as chronic pain and iatrogenic prescription of opioids*'. Participants from the CHRONIC PAIN group in my study did not experience significant extra-dimensional task errors when compared to participants in the HEALTHY

CONTROL group. However the participants from the METHADONE and HEROIN groups were assessed for presence of past and current pain syndromes when screened with the M.I.N.I questionnaire during the recruitment phase. The notion that chronic pain is exacerbating cognitive rigidity could not be observed in this study.

However one needs to take these results with caution as only one neuropsychological task sensitive to one aspect of cognitive flexibility was used. The IED task is sensitive to identify impairment in reactive flexibility which is defined as the inability to realign a behavioural predisposition to altered contingencies (**Grattan & Eslinger, 1989**). No neuropsychological tasks were used to determine other aspects of cognitive flexibility such as spontaneous flexibility using verbal and non-verbal fluency tasks (**Demakis & Harrison, 1997; Zinn *et al.*, 2004**). Switching tasks, in which participants undertaking two or more tasks that run alternately in a rapid fashion, may help to clarify the nature of deficits, if any, in cognitive flexibility in opioid dependent individuals. As a behavioural addiction with clinical and phenomenological similarities to substance addiction, recreational and pathological gambling represent models for studying the neurobiology of addiction especially cognitive flexibility, without the confounding deleterious brain effects which may occur from chronic substance abuse (**Odlaug *et al.*, 2011**) (Chapter 7).

Conclusion

Chronic opioid use or opioid dependence is not associated with deficits in cognitive flexibility or cognitive rigidity. In this study cognitive flexibility did not improve or deteriorate following periods of stability with the dependence and injecting status not contributing to the causation or deterioration of the condition.

Chapter 6: Results-Neuropsychological functioning in men with a history of chronic opioid use: Memory and Learning

Background

This chapter aims to incorporate three interrelated memory and learning neuropsychological domains. They include attentional bias and/or sustained attention, short term memory (STM) and long term memory (LTM) (Table 6.1 and Chapter 1).

Table 6.1: Memory domains.

Main Domain	Subtypes	Other names	Definition	Examples of test
Directed Attention/Registration	Sensory Peripheral Store or Sensory Memory	Visual or Iconic Memory	Retains large amount of information	
		Auditory or Echoic Memory		
Short Term Memory	Immediate Memory	Verbal Memory	Reproduction, recognition or recall of information directly or some time after presentation	LMT, RAVLT, CVLT, WAIS-III, VRM, WMSR, WRM, GNT, DFDBT, TBT
		Visuospatial Memory	Allow information to be evaluated and perhaps stored longer through rehearsal and coding	SWM, SSP, DMS, PRM, PAL, BVRT, PAL, SRM, WMSR, RCFT, PASAT, WAIS-III
Long Term Memory	Explicit (Declarative) Memory	Autobiographical, Episodic or Event Memory	Records details salient to individual's life. Needs conscious thinking. 'Knowing that'	PRM, SRM, CVLT, RAVLT, PAL, RCFT, WMSR, WAIS-III (Vocabulary)
		Semantic Memory	Meaning of words and concepts or facts	RCFT, COWAT, GNT, WMSR, RBMT
	Implicit (Non-Declarative) or Procedural Memory	(1) Motor skill training	Does not need conscious thinking. 'Knowing how'	
		(2) Priming or classical conditioning		

BVRT=Benton Visual Retention Test, COWAT= Controlled Oral Word Association Test, CVLT= California Verbal Learning Test, DFDBT= Digit Forward and Digit Backwards Test, DMS=Delayed Matching to Sample (CANTAB), GNT=Graded Name Test (CANTAB), LMT= Logical memory Test, SRM=Spatial Recognition Memory (CANTAB), PAL= Paired Associate Learning (CANTAB), PASAT= Paced Auditory Serial Addition Task, PRM= Pattern Recognition Memory (CANTAB), RAVLT= Rey Auditory Verbal Learning Test, RBMT= Rivermead Behavioural Memory Test, RCFT= Rey Complex Figure Test, SWM=Spatial Working Memory (CANTAB), SSP=Spatial Span (CANTAB), TBT= Two Back Test, VRM= Verbal Recognition Memory (CANTAB), WAIS-III= Wechsler Adult Intelligence Scale Third Edition, WMSR= Wechsler Memory Scale Revised, WRM= Word Recognition Memory.

Baddeley (1999; 2000) used the term ‘working memory’ rather than STM to describe the memory system that allows us to hold and manipulate stored information ‘on-line’. Working memory allows relevant information from our long term store to be brought in and used with current mental processing. It is not unitary, rather it is divided into three subsystems – the central executive and its’ two slave systems, the phonological loop and the visuospatial sketch-pad. The central executive is like the ‘supervisory attentional system’ proposed by **Norman & Shallice (1986)**. This ‘supervisory attentional system’ and/or ‘buffer zone’ is involved in planning and attentional control, linking the ‘slave systems to LTM. The phonological loop serves to hold and refresh an articulation (e.g., mentally rehearsing a phone number) while the visuo-spatial sketch-pad allows location and visual information to be held (**Baddeley, 1986; 1998**) (**Table 1.2**).

The neural substrates of memory and learning are among the major circuits undergoing aberrant neuro-adaptations in response to chronic drug exposure (**Volkow et al., 2004**). Different memory systems have been proposed to be involved in drug addiction. The frontal lobes have been suggested as important in working memory with the Broca’s area related to the phonological loop (**Gazzaniga et al., 2002**). The declarative memory system (knowing what, where, and when) is generally associated with circuits that encompass the medial temporal lobe (e.g. the hippocampus and perirhinal and entorhinal cortices), anterior thalamic nuclei, regions of the association cortex, and prefrontal cortex (PFC) (**Mayes et al., 2007**). The procedural memory (knowing how) has been linked with structures implicated in sensorimotor function, including sensory neocortex, motor cortex, striatum (caudate–putamen), and cerebellum (**Squire et al. 1993; White, 1996**). Classical conditioning and/or emotional memory may depend on other structures in the limbic system, including the amygdala and perhaps the nucleus accumbens (**Robbins et al., 2008**).

Learning and memory impairments have been identified in chronic amphetamine, methamphetamine users (**Ersche et al., 2006a; Gonzalez et al., 2004; Hoffman et al., 2006; Kalechstein et al., 2003; Moon et al., 2007; Ornstein et al., 2000; Rippeth et**

al., 2004; Simon *et al.*, 2002; Woods *et al.*, 2005), alcohol, opioids, ecstasy (MDMA) and cannabis users (Fernandez-Serrano *et al.*, 2010a) with mixed evidence that performance improves following long term abstinence (Fernandez-Serrano *et al.*, 2010a; Wang *et al.*, 2004).

In addition impairment in attention (attentional bias) has been observed in opioid dependent individuals (Lubman *et al.*, 2000; Mariseen *et al.*, 2006). Impairment in short and long term memory associated with chronic opioid use was considered as either related to generalised or specific effects of substance misuse (Fernandez-Serrano *et al.*, 2010b). While a number of studies identified various aspects of memory impairment (Amir & Bahri, 1994; Darke *et al.*, 2000; Ornstein *et al.*, 2000; Ersche *et al.*, 2006a; Papageorgiou *et al.*, 2004; Pirastu *et al.*, 2006; Soyka *et al.*, 2008; Prosser *et al.*, 2006), others did not find memory deficits in chronic opioid users (Fishbein *et al.*, 2007; Rapeli *et al.*, 2006; Rounsaville *et al.*, 1982) (Table 6.2).

Table 6.2: Chronic opioid use and memory. Previous research findings*.

Neuropsychological domain	Illicit chronic heroin use	Abstinent ex-heroin use	Methadone use	Other opioid use ¹	Chronic opioid dependence
Sustained Attention	McNairy <i>et al</i> (1984)↔ Stevens <i>et al</i> (2007)↓	Verdejo-Garcia <i>et al</i> (2007a)↓ Mintzer <i>et al</i> (2005)↓	Darke <i>et al</i> (2000)↓ Specka <i>et al</i> (2000)↓ Mintzer <i>et al</i> (2005)↓ Rounsaville <i>et al</i> (1982)↔ Soyka <i>et al</i> (2008)↓	Soyka <i>et al</i> (2008)↓ Sjogren <i>et al</i> (2005)↓ Jamieson <i>et al</i> (2003)↔ Tassain <i>et al</i> (2003)↔ Vainio <i>et al</i> (1995)↔ Schindler <i>et al</i> (2004)↓	
Short term memory	McNairy <i>et al</i> (1984)↓ Stevens <i>et al</i> (2007)↓	Verdejo-Garcia <i>et al</i> (2007a)↓ Fishbein <i>et al</i> (2007a)↔	Darke <i>et al</i> (2000)↓ Mintzer <i>et al</i> (2005)↔ Prosser <i>et al</i> (2006)↓ Pirastu <i>et al</i> (2006)↓ Soyka <i>et al</i> (2008)↓	Pirastu <i>et al</i> (2006)↓ Soyka <i>et al</i> (2008)↓ Tassain <i>et al</i> (2003)↔	Ersche <i>et al</i> (2006a)↓ Ornstein <i>et al</i> (2000)↓
Long term memory	Stevens <i>et al</i> (2007)↓		Darke <i>et al</i> (2000)↓	Tassain <i>et al</i> (2003)↔	Ersche <i>et al</i> (2006a)↓ Ornstein <i>et al</i> (2000)↓

*= $p < 0.05$, ↔ = no difference in memory performance; ↓ = neuropsychological (memory) deficits present, ↑ = improvement in memory performance when compared to healthy controls, Other opioid use¹ = buprenorphine, morphine, oxycodone and/or tramadol.

Most studies did not find associations of memory deficits with the amount of opioids consumed or the duration of opioid use (Ersche *et al.*, 2006a; Prosser *et al.*, 2006; Rounsaville *et al.*, 1982). By contrast, improved memory function has been reported following two months of methadone-maintenance treatment (Gruber *et al.*, 2006).

In light of the previous research in the area of opioid dependent use and neuropsychology, the present study set out to expand on the current limited knowledge base by comparing the level of neuropsychological function in memory and learning on chronic heroin, methadone and other opioids in a male population compared to non- substance using healthy controls as explained in Chapter 3 of this thesis. This will help test the hypothesis (1):

(1) Is chronic opioid dependence associated with neuropsychological impairment reflected in altered performance on measures of memory and learning?

As previously described in Chapter 4 and 5 at least three factors were considered to be related to drug taking which may exert an important influence over neuropsychological performance. These include: (1) duration of opioid use, (2) level of opioid receptor occupancy during behavioural testing-(a) during intoxication, (b) during withdrawal and (c) during stable methadone maintenance and (3) injecting status. Therefore the next two related hypothesis (2 & 3) to test are:

(2) In patients with chronic opioid dependence, is injection status associated with neuropsychological impairment as reflected in altered performance on measures of memory and learning?

(3) In patients with chronic opioid dependence is the degree of acute opioid exposure (acute intoxication, withdrawal or stable initial exposure to methadone), or duration of opioid exposure (period of methadone maintenance) associated with neuropsychological impairment as reflected in altered performance on measures of memory and learning?

Statistical considerations

Basic statistical considerations have been described in Chapter 2. The data from the DMS and SRM tests met assumptions of normality and homogeneity of variance. However the PAL and PRM tests did not meet assumptions and to stabilise variance and diminish *skewness* and *kurtosis*, the PRM data was subjected to square root (*SQRT*) transformation and the PAL data was subjected to logarithmic (*log10*) transformation (Fields, 2009).

(1) Testing hypothesis 1 and 2

Data were initially analyzed using univariate or repeated measures ANCOVA with a *between subject factor* of GROUP (HEROIN vs. CHRONIC PAIN vs. METHADONE vs. HEALTHY CONTROL) and NART, age in years, SIMD, total Fagerström score, years in education and past alcohol use in years as covariates.

Further *a priori* subgroup analyses for the DMS, PAL, PRM, and SRM tests were conducted using (1) a two-group factor reflecting DEPENDENCE (HEROIN and METHADONE groups vs. CHRONIC PAIN and HEALTHY CONTROL groups) and (2) a two-group factor reflecting lifetime INJECTING (HEROIN and METHADONE injecting vs. HEROIN and METHADONE never injecting groups) separately as *between subject factors*.

Behavioural data from the DMS and PAL were further analysed using a mixed-model analysis of variance (ANCOVA) with GROUP (HEROIN vs. METHADONE vs. CHRONIC PAIN vs. HEALTHY CONTROL) as a between- subjects fixed factor, and *difficulty* (expressed by the 0.4 and 12 second delay stages in the DMS test and the 1-3, 6 or 8 shape stages in the PAL test) as *within-subjects factors*.

Between-group effects in the ANCOVA models were analysed as follows. A planned comparison between the HEALTHY CONTROL and three experimental groups (HEROIN, METHADONE and CHRONIC PAIN) was used to detect any difference in performance. In this four-group model, significant *between-group effects* were investigated using pair-wise comparisons with *Bonferroni* correction procedure. Effect sizes for the group comparisons were calculated using Cohen's *d* (Cohen, 1988).

(2) Testing hypothesis 3

Repeated measures ANCOVA was used to evaluate DMS, PAL, PRM and SRM performance between the HEROIN group participants at baseline (whilst on illicit heroin), in controlled opioid withdrawal and subsequently when stabilised on methadone according to the tolerance testing procedure protocol with presumed

opioid receptor occupancy state as a *within subject factor* to determine whether performance on any of these tasks was modified by different degrees of opioid receptor occupancy (heroin, withdrawal and stable on methadone).

Similarly repeated measures ANCOVA was performed for the METHADONE group at baseline and at 6 months follow up with DURATION as a *within subject factor* to determine whether any aspects of performance improved or deteriorated with time and continued exposure to chronic, sustained released opioid (methadone). .

The homogeneity of variance across groups in repeated-measures design ANCOVAs was assessed by the Mauchly Sphericity Test (**Mauchly, 1940**). Where data sets significantly ($p < 0.05$) violated this requirement for a repeated-measures design ANCOVA, the Greenhouse Geisser Epsilon (ϵ) correction parameter for degrees of freedom (**Greenhouse & Geisser, 1959; Winer *et al.*, 1991**) was used to calculate a more conservative p value for each F ratio.

Results

All subjects completed all of the tests. Mean performance (not adjusted for covariates), statistical comparisons and effect sizes (d) for each task, for the HEROIN, METHADONE, CHRONIC PAIN and HEALTHY CONTROL groups, are summarised in **Tables 6.3**.

Table 6.3: Summary of baseline neuropsychological findings for memory and learning (not adjusted for covariates).

	HEROIN N=24	METHADONE N=29	CHRONIC PAIN N=28	HEALTHY CONTROL N=28		
Memory and Learning	Mean (s.d)	Mean (s.d)	Mean (s.d)	Mean (s.d)	<i>Sig.</i>	<i>d</i>
Delayed Matching to Sample (DMS)						
Total Number of Correct Responses (all delays)	22.04 (3.59)	25.76 (2.87)	25.39 (3.04)	27.43 (1.89)	P>H*** C>H***	1.00 1.87
Mean Correct Latency (all delays)	3630.61(922.64)	4372.35 (1579.98)	3310.22(1049.63)	3536.67(745.99)	M>P**	0.79
Paired Associate Learning (PAL) (log10)						
Total Errors (Adjusted)	0.22 (0.45)	0.46 (0.64)	0.01 (0.06)	0.00 (0.00)	NS	
Mean Errors to Success	0.51 (0.26)	0.42 (0.19)	0.45 (0.27)	0.29 (0.19)	C<H*	0.97
Mean Trials to Success	0.45 (0.09)	0.41 (0.06)	0.43 (0.09)	0.37 (0.05)	C<H*	1.10
Memory Score	1.23 (0.11)	1.30 (0.06)	1.27 (0.08)	1.33 (0.06)	C>H***	1.13
Stages Completed	0.94 (0.03)	0.95 (0.02)	0.95 (0.02)	0.95 (0.00)	NS	
Stages complete 1 st trial	0.79 (0.08)	0.84 (0.05)	0.82 (0.07)	0.87 (0.04)	C>H***	1.26
Pattern Recognition Memory (PRM) (SQRT)						
Percentage Trials						
Correct	9.18 (0.69)	9.27 (0.51)	9.26 (0.49)	9.64 (0.46)	C>H*	0.78
Incorrect	3.37 (1.97)	3.46 (1.46)	3.43 (1.52)	1.97 (1.74)	C<H* C<M*	0.75 0.92
Correct Response Latency						
Correct	45.82 (5.36)	47.88 (5.98)	46.37 (6.74)	46.60 (5.56)	NS	
Incorrect	49.80 (11.99)	54.48 (11.74)	50.22 (10.76)	50.15 (8.96)	NS	
Spatial Recognition Memory (SRM)						
Number of Trials						
Correct	15.58 (2.21)	16.48 (1.94)	15.89 (1.77)	17.75 (1.51)	C>H***	1.15
Incorrect	4.42 (2.21)	3.52 (1.94)	4.11 (1.77)	2.25 (1.51)	C<M***	1.15
Mean Latency						
Correct	1979.04 (432.81)	2358.89 (810.68)	2035.71 (505.51)	2040.19 (469.3)	NS	
Incorrect	2172 (878.02)	2520.36 (966.13)	2199.65 (737.71)	2456.38 (122.41)	NS	

d= effect size, *SQRT*= square root transformation; *log10* = logarithmic 10 transformation, *Sig*= significance, * = $p < 0.01$, ** = $p < 0.005$, *** = $p < 0.001$, NS= no significant impairment in neuropsychological outcomes with $p < 0.01$, H=HEROIN Group, P=CHRONIC PAIN Group, M= METHADONE Group, C=HEALTHY CONTROL Group.

- Delayed Matching to Sample (DMS)

There was a significant GROUP [$F(3,100) = 10.3, p < 0.001$] effect on the percentage of correct responses but a non-significant GROUP [$F(3,100) = 2.6, p = .06$] trend on mean correct latency response. *Post hoc Bonferroni* comparison showed participants from the HEROIN group significantly made more errors than did the HEALTHY CONTROL group in the 0 ($p < 0.005$), 4 ($p < 0.001$) and 12 second ($p < 0.001$) delay stages, from the CHRONIC PAIN group for the 4 ($p < 0.01$) and 12 ($p < 0.005$) second delay stages and from the METHADONE group for 0 ($p < 0.005$), 4 ($p < 0.005$) and 12 ($p < 0.001$) second delay stages (**Figure 6.1**).

There were no significant DEPENDENCE status effects (average speed of responses [$F(1,102) = 3.8, p = .05$] and percentage of correct responses [$F(1,102) = 1.1, p = .30$] or INJECTING [$F < 1$] on DMS outcomes. There were also no significant interactions [$F < 1$].

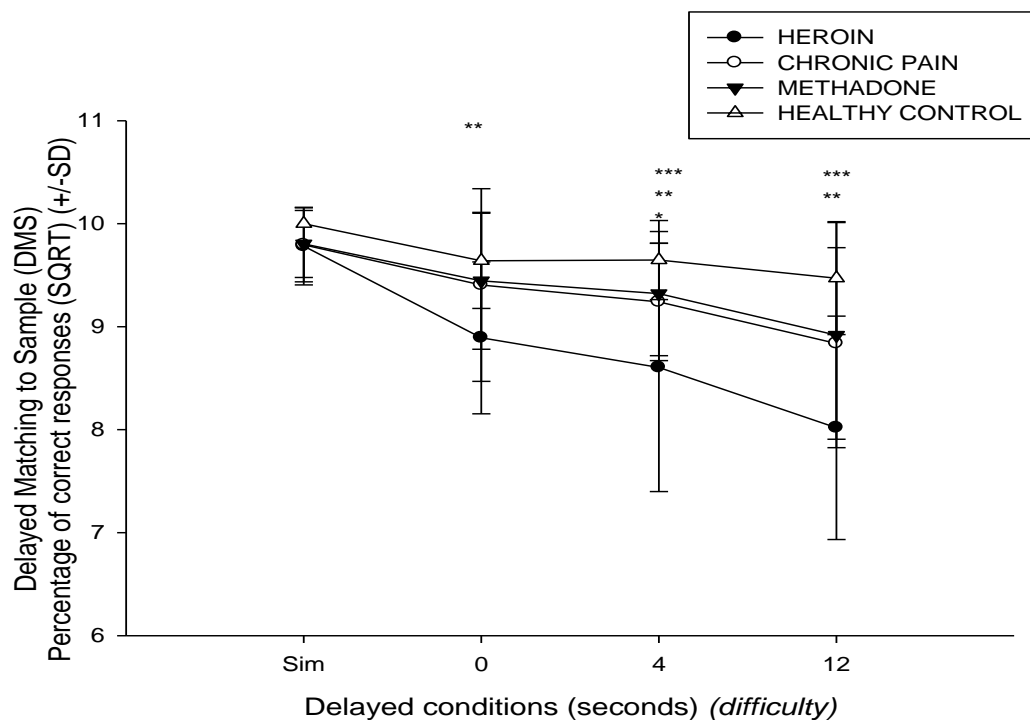


Figure 6.1: DMS-Percentage of correct responses at different delay conditions. There was a significant GROUP [$F(3,100) = 10.3, p < 0.001$] *Post-hoc Bonferroni* comparison showed participants from the HEROIN group significantly made more errors than did the HEALTHY CONTROL group in the 0 (** $p < 0.005$), 4 (** $p < 0.001$) and 12 second (** $p < 0.001$) delay stages, from the CHRONIC PAIN group for the 4 (* $p < 0.01$) and 12 (** $p < 0.005$) second delay stages and from the METHADONE group for 0 (** $p < 0.005$), 4 (** $p < 0.005$) and 12 (** $p < 0.001$) second delay stages. Sim= Simultaneous condition, SD= Standard Deviation.

Overall the HEROIN group significantly made more errors at all three *difficulty* levels but spend the same time as any of the other three groups in the length taken to make a decision. When the HEROIN group was tested during different *opioid receptor occupancy states* there was a significant effect of opioid load on mean correct latency [$F(2,34.22)=10.5, p<0.001$]. *Post hoc Bonferroni* comparison showed a significant improvement at the 12 second delay stage ($p<0.001$) and a non-significant trend at the 0 second ($p=.05$) and 4 second ($p=.07$) delay condition stages. The pattern of improvement was significantly shifting towards the stable methadone stage when compared to the withdrawal stage ($p<0.005$) and illicit heroin stage ($p<0.001$).

Overall the METHADONE group was significantly selecting the right stimulus when compared to the HEROIN group at baseline. There was a non-significant trend ($p<0.05$) for the METHADONE group to improve in selecting the right stimulus following prolonged exposure to a stable dose of methadone.

Table 6.4: Summary of results from analysis of DMS outcomes¹. Unless specified significance is with HEALTHY CONTROL and/or CHRONIC PAIN groups*.

Delayed Matching to Sample (DMS)	HEROIN vs METHADONE vs CHRONIC PAIN vs HEALTHY CONTROL	Opioid DEPENDENCE (OD) vs Non- Opioid DEPENDENCE (Non-OD)	INJECTING (INJ) vs non-injecting
Correct Responses (Simultaneous, 0, 4 and 12 sec. delays)	↓HEROIN (also H>M) at 0, 4 and 12 sec. delays	↔	↔
Speed of responses (mean correct latencies at 0,4 and 12 sec. delays)	↔	↔	↔

*= significant effects with $p<0.01$, ↓=significant neuropsychological deficits present, ↔= no significant neuropsychological deficits present, ¹= ANCOVA 'between subject factor' of GROUP, DEPENDENCE and INJECTING analysed separately, H= HEROIN, M= METHADONE.

- Paired Associate Learning (PAL)

There was a no GROUP effect for: total number of errors [$F<1$], total trials to locate the pattern correctly [$F(3,102)=1.5, p=.23$], stages completed on first trial [$F(3,102)=3.2, p=.03$] and memory score [$F(3,102)=3.4, p=.02$] (**Figure 6.2**).

There were no significant DEPENDENCE effects or INJECTING effects [$F < 1$] on all outcome measures of the PAL task. There were also no significant interactions in the DEPENDENCE [$F(4,326.81) = 3.1, p = .03$] and INJECTING [$F < 1$] status.

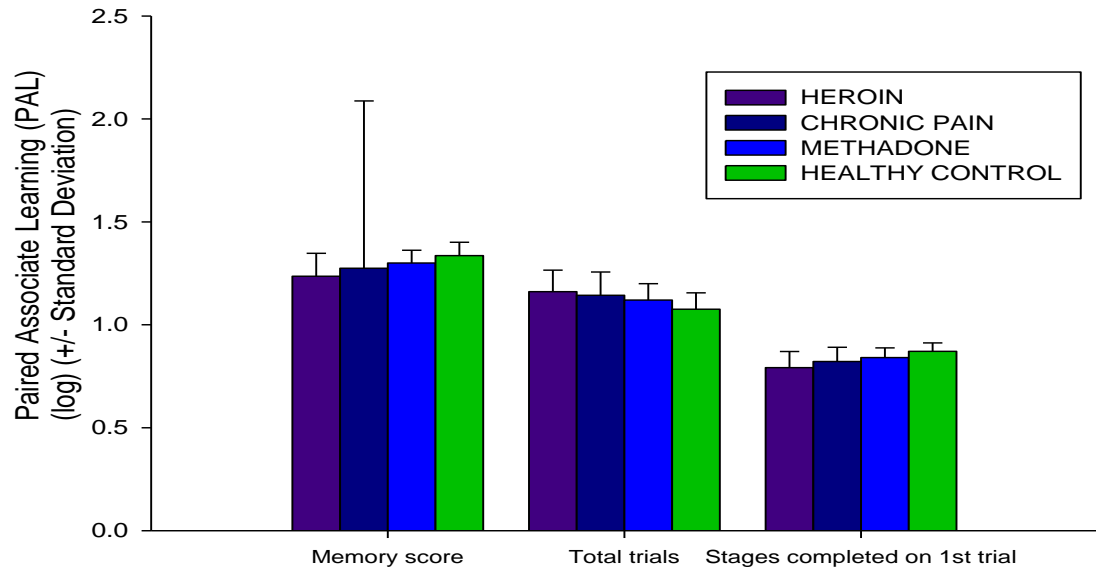


Figure 6.2: PAL outcomes in HEROIN, METHADONE, CHRONIC PAIN and HEALTHY CONTROL groups. There was a non-significant GROUP trend for: Total trials to locate the pattern correctly [$F(3,102) = 1.5, p = .23$], Stages completed on first trial [$F(3,102) = 3.2, p = .03$] and Memory score [$F(3,102) = 3.4, p = .02$].

Overall the HEROIN group did not significantly experience memory problems. When the HEROIN group was tested during different *opioid receptor occupancy states* there was no effect of opioid load on PAL outcomes.

Overall the METHADONE group did not significantly experience memory problems. There was no significant additional effect on all PAL outcomes in the METHADONE group following prolonged exposure to a stable dose of methadone.

Table 6.5: Summary of results from analysis of PAL outcomes¹. Unless specified significance is with HEALTHY CONTROL and/or CHRONIC PAIN groups*.

Paired Associate Learning (PAL)	HEROIN vs METHADONE vs CHRONIC PAIN vs HEALTHY CONTROL	Opioid DEPENDENCE (OD) vs Non- Opioid DEPENDENCE	INJECTING (INJ) vs non- injecting
Total Errors	↔	↔	↔
Total Trials to Locate Patterns Correctly	↔	↔	↔
Stages Completed on First Trial	↔	↔	↔
Memory Score	↔	↔	↔

*= significant effects with $p < 0.01$, ↓=significant neuropsychological deficits present, ↔= no significant neuropsychological deficits present, ¹ = ANCOVA 'between subject factor' of GROUP, DEPENDENCE and INJECTING analysed separately.

- Pattern Recognition Memory (PRM)

There were no significant GROUP effects on the number of correct trials [$F < 1$] and mean response latency [$F < 1$]. There were also no significant DEPENDENCE effect [$F < 1$] and INJECTING effects [$F < 1$] on the number of correct trials and mean response latency.

When the participants from the HEROIN group were tested during different *opioid receptor occupancy states* there was no effect of opioid load. There was also no additional effect on all PRM outcomes in the METHADONE group following prolonged exposure to a stable dose of methadone.

Table 6.6: Summary of results from analysis of PRM outcomes¹. Unless specified significance is with HEALTHY CONTROL and/or CHRONIC PAIN groups*.

Pattern Recognition Memory (PRM)	HEROIN vs METHADONE vs CHRONIC PAIN vs HEALTHY CONTROL	Opioid DEPENDENCE (OD) vs Non- Opioid DEPENDENCE	INJECTING (INJ) vs non- injecting
Number of Correct Trials	↔	↔	↔
Mean Response Latency	↔	↔	↔

*= significant effects with $p < 0.01$, ↔= no significant neuropsychological deficits present, ¹ = ANCOVA 'between subject factor' of GROUP, DEPENDENCE and INJECTING analysed separately.

- Spatial Recognition Memory (SRM)

There were no significant GROUP effects on the number of correct trials [$F(3,102)=3.6, p=.02$] and mean response latency [$F(3,102)=2.8, p=.04$]. There were also no significant DEPENDENCE and INJECTING status [$F<1$] effects on all the SRM outcomes.

When the HEROIN group was tested during different *opioid receptor occupancy states* there was no effect of opioid load. There was also no additional effect on all SRM outcomes in the METHADONE group following prolonged exposure to a stable dose of methadone.

Table 6.7: Summary of results from analysis of SRM outcomes¹. Unless specified significance is with HEALTHY CONTROL and/or CHRONIC PAIN groups*.

Spatial Recognition Memory (SRM)	HEROIN vs METHADONE vs CHRONIC PAIN vs HEALTHYCONTROL	Opioid DEPENDENCE (OD) vs Non- Opioid DEPENDENCE	INJECTING (INJ) vs non- injecting
Number of Correct Trials	↔	↔	↔
Mean Response Latency	↔	↔	↔

*= significant effects with $p<0.01$, ↔= no significant neuropsychological deficits present, ¹ ANCOVA 'between subject factor' of GROUP, DEPENDENCE and INJECTING analysed separately.

Discussion

Overall this study observed opioid taking groups performing on tasks which were visual and/or non- verbal in function and sensitive to working memory that included components of short and long term memory. Using Baddeley's model of working memory the cognitive tests sensitive to the spatial executive memory function and visuospatial strategy were tested using the SSP and SWM (Chapter 4) (**Baddeley, 1999**). The analysis showed that the HEROIN groups made significantly more errors impaired planning problems especially when a high level of difficulty was presented. The METHADONE group struggled to recall longer sequences presented (span length) indicating short and long term memory deficits.

Using Braddeley's working memory model this chapter analysed the DMS, PAL, PRM and SRM tasks testing opioid dependent and opioid using individuals. These cognitive

tasks are sensitive to both phonological loop and visuospatial sketch pad slave system (Baddeley, 1999).

Table 6.8 summarises the outcomes of opioid using groups and associated, if any, memory deficits. Overall it was only the HEROIN group that showed significant deficits in visuospatial working memory ability at the $p<0.01$ significance level. There were other deficits observed in both HEROIN and METHADONE groups but the outcomes only reached the 95% level of confidence. The DEPENDENCE and INJECTING status showed latency problems in the DMS task but again did not reach $p<0.01$ significance level.

Table 6.8 : Summary of outcomes of opioid using groups and neuropsychological functioning in memory compared with HEALTHY CONTROL group.*

Neuropsychological domain	Tests	HEROIN	METHADONE	CHRONIC PAIN	Opioid DEPENDENCE	INJECTING group
MEMORY and LEARNING						
Visual immediate and working memory (1)	DMS	Number of Correct Responses	No impairment	No impairment	No impairment	No impairment
Visual immediate and working memory (2)	PAL, PRM, SRM	No Impairment	No Impairment	No impairment	No impairment	No impairment

*= $p<0.01$, no impairment= no difference in neuropsychological performance when compared to healthy controls, d = effect size, DMS= Delayed Matching to Sample, PAL=Paired Associate Learning, PRM= Pattern Recognition Memory, SRM= Spatial Recognition Memory.

The simultaneous condition of the DMS may be conceptualised as a control task for the delayed matching conditions. The simultaneous and delay conditions have the same neurocognitive requirements except that the ability to internally represent the stimuli is required in the delay conditions (Pantelis *et al.*, 2001). In this study the HEROIN group did not perform significantly different between the simultaneous and delayed matched conditions. The participants in the HEROIN group significantly performed poorly compared to the other three groups at the 0, 4 and 12 second delay stages indicating poor memory ability but improved when stabilised on methadone.

The PAL assesses visual working memory and visuospatial associative learning (explicit or declarative memory). The METHADONE group experienced long term memory problems on the PAL but did not reach significance of $p < 0.01$ level (**Table 6.8**). The PRM and SRM are often used before the PAL test in order to help to train the participant for the PAL tasks. The PRM has been shown to be sensitive to temporal lobe and hippocampus and not the frontal lobe, whereas the SRM showed the opposite pattern of morphological sensitivity (**Owen *et al*, 1995**). In this study the HEROIN group but not the METHADONE group experienced memory deficits but again did not reach the $p < 0.01$ significance levels (**Table 6.8**).

Overall both the HEROIN and the METHADONE groups experienced memory deficits but most did not reach significance ($p < 0.01$). Therefore the hypothesis that chronic opioid dependence is associated with neuropsychological impairment reflected in altered performance on measures of memory and learning has only been partially confirmed with participants in the HEROIN group experiencing significant ($p < 0.01$) non verbal memory problems on the DMS task. Injecting status, the degree of acute opioid exposure, and duration of opioid exposure did not significantly alter performance on measures of memory.

Ersche *et al*. (2006 & 2005) compared a group of opioid dependent individuals with a group of amphetamine dependent individuals across a number of neuropsychological domains. The opioid dependent group consisted largely of methadone maintenance patients and current illicit heroin users, as well as participants receiving prescribed buprenorphine, dihydrocodeine, diamorphine and morphine sulphate. Control groups included drug free controls, drug free ex-opioid users and drug-free ex-amphetamine users. The study utilised the PAL and the PRM to test working visuospatial memory. On both these tests on memory, current and former opioid users performed at a level that was significantly ($p < 0.05$) poorer than controls supporting the notion that the neuropsychological deficits observed in chronic opioid users were not a direct result of the opioid itself, but rather were a consequence of the factors associated with long-term drug abuse.

However **Ornstein *et al.* (2000)** conducted a study which aimed to clarify the notion that there exists a distinct profile of neuropsychological impairment which is common to heroin dependent individuals. In this study, a group of participants whose primary drug of abuse was heroin and most also treated with methadone were compared to a group who primarily used amphetamine. A third group of drug-free control participants was matched to the other two groups for age and pre-morbid intellectual functioning. The assessment consisted of a number of subtests chosen from the CANTAB computerised test battery including SRM, SWM and PRM tasks. This study found that, relative to controls, the heroin group were found to be significantly impaired in visuospatial recognition memory. These results pointed to the existence of a diverse pattern of neuropsychological impairment in heroin dependent individuals who were still using heroin.

Memory and learning was tested using the DMS to twenty five male heroin dependent individuals and compared to twenty six polydrug abusers abstinent for more than 3 months and another twenty six non- drug using healthy male controls. There was a moderate but significant impairment in working memory and sustained attention in the heroin group (**Stevens *et al.*, 2007**).

Compared to these previous studies, which utilised the same neuropsychological task as this study, impairment in memory is a significant problem during most opioid related states but most distinctively in the heroin group. This was partially observed in the current study. The notion that memory improves with stability or cessation of opioid use needs further investigation.

Conclusion

Participants from the HEROIN and METHADONE but not the CHRONIC PAIN groups experienced visuo-spatial memory problems especially at a 12 second delay stage of difficulty of the DMS task indicative of long term memory problems. These observations do not indicate deficits as a result of chronic opioid use but rather due to the use of heroin with potential improvement after 3 weeks stability with

methadone use. Dependence and injecting status do not contribute to the causation or deterioration of any of the identified deficits.

Chapter 7: Summary and general discussion, limitations and future directions.

Summary and general discussion

The work presented in this thesis describes the neuropsychological heterogeneity defined within a group of rigorously diagnosed opioid dependent and non-opioid dependent populations. Specific experimental findings were discussed in some detail at the end of Chapters 4, 5 and 6. The purpose of this chapter, therefore, is to bring these findings together into a more general discussion, to consider the limitations of the study and to suggest potential avenues for further investigation. The main hypotheses and findings from each chapter are summarised in **Tables 7.1-7.3**.

Overall chronic opioid dependence is associated with neuropsychological impairment reflected in altered performance on measures of risk taking and strategic planning. This is indicative of trait vulnerability for drug taking and/or dependence rather than due to chronic opioid use as no neuropsychological impairments were recorded with participants from the CHRONIC PAIN group. These impairments were more evident with the HEROIN participants. Motor impulsivity and visuo-spatial memory impairments in HEROIN group improved after three weeks stability with methadone. There was no reduced intellectual function or impairment with cognitive flexibility in participants with a history of chronic opioid dependence. Dependence and injecting status did not contribute to the causation or deterioration of any of the identified impairments.

This study complement evidence from previous studies as highlighted in the systematic review in Chapter 1 of this thesis. Studies of current and abstinent chronic opioid users (illicit heroin users, patients prescribed methadone for illicit opioid dependence and patients taking opioids as part of the management of chronic pain) have identified performance deficits in measures of executive functioning and memory. These have included impairments in cognitive and motor impulsivity, strategic planning, cognitive flexibility and memory. Similar to results from this study the systematic review highlighted that impulsivity problems seem to be the 'core' or

residual deficit of the dependence phenotype. The literature also suggested that these neuropsychological deficits may be subject to at least partial recovery following initiation of methadone or total withdrawal from any opioids.

Table 7.1: Hypothesis and main findings from Chapter 4: Neuropsychological impairments on performance in cognitive impulsivity.

Chapter 4		
Hypothesis	Outcome	Comments
Is chronic opioid dependence associated with neuropsychological impairment reflected in altered performance on measures of impulsivity and risk taking?	Partially Supported	<p>HEROIN users placed higher bets earlier and risked more. HEROIN users also showed motor impulsivity shown by deficits in commission errors of the AGN task. HEROIN users also showed poor strategic planning as reflected by number of errors at highest level of difficulty (5 move stage problem) on the SOC and on the SSP (but not the SWM) task.</p> <p>METHADONE users deliberated longer and placed higher bets earlier. METHADONE users were more inattentive and showed poor strategic planning as reflected by number of errors at highest level of difficulty (5 move stage problem) on the SOC.</p> <p>The participants in the CHRONIC PAIN group showed a non-significant trend in poor strategic planning as reflected by number of errors at highest level of difficulty (5 move stage problem) on the SOC but not in other tasks. This was not observed when tested with the SSP and SWM task.</p>
In patients with chronic opioid dependence, is injection status associated with neuropsychological impairment as reflected in altered performance on measures of impulsivity and risk taking?	Not Supported	
In patients with chronic opioid dependence is the degree of acute opioid exposure (acute intoxication, withdrawal or stable initial exposure to methadone), or duration of opioid exposure (period of methadone maintenance) associated with neuropsychological impairment as reflected in altered performance on measures of impulsivity and risk taking?	Partially Supported	Motor impulsivity in HEROIN improved when stabilised with methadone.

Table 7.2: Hypothesis and main findings from Chapter 5: Neuropsychological impairments on performance in cognitive flexibility .

Chapter 5		
Hypothesis	Outcome	Comments
Is chronic opioid dependence associated with neuropsychological impairment reflected in altered performance on measures of cognitive flexibility?	Not Supported	HEROIN users made more errors compared to other groups on the overall IED task but both HEROIN and METHADONE users did not experience deficits in cognitive flexibility
In patients with chronic opioid dependent, is injection status associated with neuropsychological impairment as reflected in altered performance on measures of cognitive flexibility?	Not Supported	
In patients with chronic opioid dependent is the degree of acute opioid exposure (acute intoxication, withdrawal or stable initial exposure to methadone), or duration of opioid exposure (period of methadone maintenance) associated with neuropsychological impairment as reflected in altered performance on measures of cognitive flexibility?	Not Supported	

Table 7.2: Hypothesis and main findings from Chapter 6: Neuropsychological impairments on performance in learning and memory.

Chapter 6		
Hypothesis	Outcome	Comments
Is chronic opioid dependence associated with neuropsychological impairment reflected in altered performance on measures of learning and memory?	Partially supported	<p>HEROIN users experienced deficits in visuo-spatial memory at the 0,4,12 second delay stages of the DMS. This was not complemented with the PAL, PRM and SRM tasks which showed no memory deficits in HEROIN users</p> <p>METHADONE users did not recall longer sequences presented on the SSP tasks indicative of memory problems. This was not complemented with the DMS, PAL, PRM and SRM tasks which showed no memory deficits in the METHADONE users</p>
In patients with chronic opioid dependent, is injection status associated with neuropsychological impairment as reflected in altered performance on measures of learning and memory?	Not Supported	
In patients with chronic opioid dependent is the degree of acute opioid exposure (acute intoxication, withdrawal or stable initial exposure to methadone), or duration of opioid exposure (period of methadone maintenance) associated with neuropsychological impairment as reflected in altered performance on measures of learning and memory?	Partially Supported	The HEROIN users showed improvement at the 12 second delay stage of the DMS when stabilised with methadone

Impulsivity, cognitive flexibility and memory

The ability to adapt to the constantly changing environment needs not only the suppression of inappropriate behaviour associated with punishment but also the selection and maintenance of appropriate behaviour associated with reward (**Cools, 2008**). This can only be achieved through a motivated and goal directed mind that is both cognitively stable and flexible. Such processes are known to be modulated by dopamine driven circuits in the frontostriatal and limbic-striatal areas (**Alexander *et al.*, 1986**).

Healthy but highly impulsive individuals respond faster in anticipation of reward (**Wallace & Newman, 1990; Cools *et al.*, 2005**). Highly impulsive individuals also have greater difficulty with reversal based on unexpected punishment than with reversal based on unexpected reward (**Hyman, 2007; Roshan, 2008**). **Koob *et al.* (1978)** followed by **Baldo & Kelley (2007)** deconstructed 'reward' as an activating, preparatory and energising effect or 'wanting' and a consummatory and hedonic effect or 'liking' (**Robinson & Berridge, 2003**). Preparatory reward-directed behaviour is characterised by increased cognitive flexibility and exploration that could be activated by drug related cues. Meantime consummatory reward-maintaining behaviour is characterised by cognitive inflexibility, rigidity and repetitive behaviour (**Baldo & Kelley (2007)**). Together with impulsivity and cognitive flexibility, working memory is also considered as vital in the active maintenance and stabilisation of goal representations that is critical for the active suppression and selection of irrelevant and relevant behaviours (**Hyman, 2007; Roshan, 2008, Baddeley *et al.*, 1998**).

Although prior models of cognitive control and working memory have considered almost exclusively the role of the PFC, more recent theorising highlights a critical role in cognitive control for an additional brain region, the striatum (**Frank *et al.*, 2001; Zhang *et al.*, 2007; McNab & Klingberg, 2008**). A large body of work has established that the rewarding properties of addictive drugs depend on their ability to increase dopamine in synapses made by ventral tegmental area neurons on the nucleus accumbens which occupy the ventral striatum especially within the nucleus

accumbens shell region (**Wise & Bozarth, 1987; Di Chiara, 1998; Koob & Bloom, 1988; Pontieri et al., 1995**).

Specifically, whereas dopamine (D1) receptor stimulation in the PFC is thought to promote cognitive stability (**Durstewitz et al., 2000**), dopamine receptor stimulation in the striatum has been hypothesized to promote cognitive flexibility (and set shifting), by allowing the flexible updating of newly relevant goal representations (**Frank, 2005**). Increases and decreases in PFC dopamine lead to decreases and increases in striatal dopamine respectively, possibly reflecting compensatory regulation at the systems level (**Meyer-Lindenberg et al., 2005**). Thus, *'high levels of striatal dopamine that are good for cognitive flexibility might be bad for cognitive stability. Similarly, high levels of PFC dopamine that is good for cognitive stability might be bad for flexibility. One implication of this model is that cognitive stability and flexibility, mediated by prefrontal and striatal dopamine respectively, trade off in the healthy brain, where dopamine levels interact dynamically'* (**Cools, 2008**).

In the diseased brain, dopamine dysregulation in both the PFC and the striatum may independently disrupt subcomponent processes, sometimes causing the apparently paradoxical combination of instability (or impulsivity) and inflexibility (or rigidity) (**Cools, 2008**).

HEROIN participants in the study exhibited significant cognitive impulsivity and motor impulsivity together with significant impairment in executive working memory function. However the same HEROIN users did not experience significant cognitive rigidity. The presentation in the HEROIN users might indicate:

- (1) A diseased brain with striatal dopamine levels overriding PFC dopamine receptor stimulation.
- (2) A diseased brain with significant decreases in PFC dopamine levels.
- (3) A diseased brain with the dopamine regulation in both PFC and striatum independently disrupted.

Meantime METHADONE participants in the study did not significantly exhibit either cognitive impulsivity or cognitive rigidity. One can postulate that this might indicate a protective and 'healing' influence of methadone treatment with possible (partial or complete) reversal towards cognitive stability in the opioid dependent individuals as a result of long term methadone treatment.

Impulsivity as a cognitive endophenotype

Robbins *et al.* (2012) proposed a biological approach to substance misuse and dependence based on 'neurocognitive endophenotypes'. An endophenotype is operationally defined as a biomarker that is associated with illness in the population, is heritable, found in nonaffected family members especially first degree relatives at a higher rate than in the general population and primarily state-independent (manifests in an individual whether or not illness is active) (**Gershon & Goldin, 1986; Gottesman & Gould, 2003; Lebover *et al.*, 1998**).

The characterisation of neurobiological traits associated with vulnerability for substance misuse and subsequent dependence has extended to the cognitive domain. Advocates for neurocognitive endophenotypes note that these neuropsychological features appear before the disorder becomes clinically apparent, stay stable throughout its course, and do well in predicting functional outcomes (**Robbins *et al.*, 2012; Everitt *et al.*, 2008**). Eventually the scope of identifying these endophenotypes is to describe and explain substance use, abuse and dependence.

Current research has highlighted that impulsivity could be a proposed cognitive endophenotype for substance dependence, servicing as a predisposing risk factor, as well as a possible consequences of chronic substance use (**Robbins *et al.*, 2012**). High levels of impulsivity were proposed as a biomarker to the development of compulsive drug taking (**Robbins *et al.*, 2012; Ersche *et al.*, 2011a**). Such observations were based on neuropsychological and neuroimaging studies of psychostimulant dependent individuals predominantly cocaine and/or amphetamine users (**Ersche *et al.*, 2011b**). Given the complexities and heterogenous nature of this domain, cognitive endophenotyping allows further exploration to ask if such a domain is a unitary

construct (**Dalley et al., 2011**). In this thesis we subdivided impulsivity into cognitive impulsivity (reflection impulsivity and risk taking); motor impulsivity (behavioural and cognitive inhibitions); and non-planning impulsivity (reasoning and problem solving) (**Ersche et al., 2006a**). These different aspects of impulsivity were assessed by specific neuropsychological measures such as Cambridge Gambling Task for cognitive impulsivity, Affective Go NoGo for motor impulsivity and the Stockings of Cambridge for non-planning impulsivity. Whether these different measures relate to a unitary construct of impulsivity is still controversial (**Dalley et al., 2011**). .

This thesis will be the first to help start unravelling if the concept of cognitive endophenotypes identified as a result of psychostimulant based human models are in fact still valid in opioid research. This study has identified impairments in cognitive impulsivity (risk taking) and non-planning impulsivity (strategic planning). It is not correct to assume that these deficits are core addiction phenotype markers for heroin dependent individuals as this was not the intention of this study. If such markers are indeed endophenotypes than one would assume that individuals treated with methadone with a past history of heroin dependence will be experiencing the same neuropsychological impairments. This was not observed in this study.

This study therefore highlights that not only should such studies be replicated but that possibly the route to opioid dependence might necessitate different vulnerability markers than those observed in psychostimulant dependence (**Dilleen et al., 2012**). Further specific studies need to be conducted to explore further such assumptions.

Limitations

Although this study was designed to avoid many of the limitations of previous work in this field as described in Chapter 1, it is inevitable that there were still several significant limitations. These include the type of population studied; the objective measurement of substance use; acute and chronic effects of polysubstance use; and data gathering.

The population studied

Recruitment

As the study focused on recruiting males the results cannot be generalised to females. It is equally not known what the impact of ethnicity, social deprivation and age have on the neuropsychological performance in opioid dependence (**Hackman *et al.*, 2010; Hackman & Farah, 2009; Noble *et al.*, 2007; Turner & Avison, 2003; van Praag *et al.*, 2000**). The study sample, although larger than that of comparable studies and rigorously defined, included only referred and treatment seeking male population which might have introduced a Berkson (recruitment) bias (**Berkson, 1946**). This study did not attempt to seek other community opioid dependent or abusing populations sometimes categorised as 'hidden' or 'hard to reach' which would have made this study difficult and unsafe to conduct primarily due to the nature of the 'drug fuelled lifestyle'.

All opioid dependent participants had a mean duration of 7.5 years heroin use and a daily dose of 165mg morphine equivalent. Recruiting a CHRONIC PAIN group with no history of opioid dependence or illicit drug use would inevitably bias the type of population and opioid dosage used. The CHRONIC PAIN group were significantly older, more educated and employed than the HEROIN and METHADONE cohorts with a much lower mean daily dose of 59.1 mg of morphine equivalence than that of the opioid dependent participants

Sample size

While this sample was of adequate size for most of the statistical analyses, it is possible that several of the subgroup analyses, in particular those investigating the impact of injecting and opioid dependence might have been underpowered. This may have resulted in Type II errors whereby actual group differences were not recognised due to a lack of study power.

The opioid dependent cohorts (HEROIN and METHADONE groups) were matched on a series of variables such as chronicity and severity of opioid use, injecting status and

severity of the opioid dependence syndrome. The HEROIN and METHADONE cohorts recruited were representative of the treatment seeking population (non-participants and non-completers) attending services in the South East Scotland region, Scotland and UK wide. The difficulty was matching the METHADONE and HEROIN users with the CHRONIC PAIN and/or HEALTHY CONTROL groups. Therefore attempts to compensate this inevitable mismatching were minimised by using NART, age in years, Fagerström status, past alcohol use and dosage of opioid used as covariates throughout the statistical analysis.

Substance use and dependence

This study lacked objective measurements to the use of drug and alcohol use. Information on lifetime and recent use was recorded verbatim from the participants with an assumption that they are able to remember such detail and to be totally honest about their illicit behaviour. The opioid dependent population tend to underestimate their own levels of use (**Mensch & Kandel, 1988**). A more objective measurement could only have been possible if all participants had a hair analysis every six months or a serial analysis of drug and alcohol serum metabolite levels (**Fraser *et al.*, 2002**). These techniques would still not have been able to determine lifetime use which can only be achieved if prospective longitudinal studies are conducted recruiting individuals at their early teens and followed up for 10-15 years.

Neuropsychological research has shown that consumption of alcohol, benzodiazepines and psychostimulants including nicotine are important confounding variables (**Ersche *et al.*, 2007; Robbins *et al.*, 2007; Koobs & Volkow, 2010**). This study tried to use stringent criteria to exclude regular and dependent users of other psychoactive substances but this was only objectively confirmed by using drug urine analysis for pragmatic reasons aware of its limitations as discussed. Such analysis can be inappropriate as a large quantity of information is lost about the frequency of use, the amount consumed, how recent the use was or the pattern of use over a long period of time. Due to the psychoactive nature of the adulterants present in heroin seizures in Fife one is not certain what neuropsychological effects caffeine and

paracetamol have on the results of this study. It was also very difficult to recruit normal HEALTHY CONTROL participants who were also nicotine dependent.

This study also tried to operationally define acute, subacute and chronic use. It attempted to standardise the time when the participants were tested which was between 2-4 hours after the intake of either the illicit heroin, prescribed methadone or other opioids. Heroin has a different time to peak concentrations (t_{\max}) than that of methadone. The bioavailability of heroin largely depends on the route of administration. The t_{\max} of smoking heroin is 2-4 minutes with heroin's blood levels becoming undetectable after 10-70 minutes and with a bioavailability estimated between 38-53% (**Rook *et al.*, 2006**). Methadone's t_{\max} is 2.5 – 5 hours with a bioavailability ranging from 36 – 100% (**Eap *et al.*, 2002**).

There were no attempts to test heroin, methadone and other opioid users at any stage before or after the cognitive tests to determine the t_{\max} serum levels of every participant. This would have been logistically difficult due to the population recruited and the drug related lifestyle of the heroin users which would have made recruitment or even obtaining a blood specimen very difficult. It would also have been unethical and perhaps illegal to determine how much and what quality of the heroin the participants in that group needed to take prior to cognitive testing. Interpretation of the data collected is further hindered by the absence of reliable and valid measures of treatment adherence. Although assigned to methadone treatment for opioid dependence or opioid analgesics for chronic pain, it was not possible to be absolutely certain that the participants actually took their medication as prescribed, nor that other illicit drugs or alcohol were avoided throughout the treatment period.

Tolerance testing procedure provided a unique opportunity to create an equitable platform to test three different periods of opioid receptor occupancy in the HEROIN group. Timing to test the HEROIN group two weeks or more after stabilising with methadone was arbitrary with no biological foundation to it. There was also no relevant literature that could confidently show cognitive improvement or

deterioration in neuropsychological function in methadone users after six months to one year stability. This study showed neuropsychological deficits at baseline in decision making in the METHADONE group with no change when followed up after six months. One is still unable to determine if these impairments were still irreversible with a longer treatment period on methadone. A longer longitudinal study will help determine:

- (a) If methadone does help improve (all or partial) neuropsychological performance with time.
- (b) If heroin related impairments improve or not with longer periods of methadone treatment.
- (c) Determine if neuropsychological impairments present are reversible or, if some are, others are not.

Data gathering

The battery of neuropsychological tasks used was more extensive than that used in previous studies. By utilising the CANTAB tasks, it was possible to include a cohesive and comprehensive battery of tasks that are rooted in experimental and laboratory neuroscience and which included a range of built in control tasks that are usually missing from clinical neuropsychological batteries (**Robbins *et al.*, 1994; Lowe & Rabbit, 1998**). There are, however, additional tasks which tap into other aspects of neuropsychological functioning thought to be important in opioid dependence and which CANTAB does not test for. This includes tasks measuring verbal memory (**Luciana, 2003**). It is also unfortunate that this study did not utilise the CANTAB tasks specifically measuring reaction time. For pragmatic reasons it was decided not to conduct the Reaction Time task as its inclusion would have increased the session by another 30 minutes. In addition the ecological validity of CANTAB needs further investigation in order to establish the value of CANTAB tests outcomes as predictors of community functioning and levels of morbidities within the population studied (**Levaux *et al.*, 2007**).

Future directions

Seven main avenues for future studies are presented below: the use of latent variable analysis; improved and alternative sampling techniques, the issue of specificity, the use of a broader range of neuropsychological tasks; measurement across the various levels of analysis; the use of other medications; the use of broader measures of clinical outcome.

The use of latent variable analyses

Latent variable analyses are designed to examine average effects and individual differences in tandem and are therefore ideal tools to investigate the impact of these differences on neuropsychological functioning. Because they account for measurement error the latent variables generated by these techniques allow the researcher to compare groups using 'true', rather than the overall, scores. Although still relatively complex, such analyses have become much more accessible in recent years with the development of statistical packages such as Mplus and AMOS (Muthén, 2002).

The use of a latent variable approach with confirmatory factor analyses with the opioid using groups and healthy control baseline data from this study would allow one to test whether:

- (1) The tasks presumed to have either high or low executive demands did indeed separate as predicted.
- (2) Measurement invariance (i.e. did the various tasks used in the study tap the same underlying constructs for both the opioid and the healthy control groups?). If this is not true for all tasks used in the study can a subset of tasks be identified that does allow a meaningful comparison between the four groups?
- (3) There are group differences when the true (as opposed to overall) scores are used.
- (4) There is heterogeneity in neuropsychological function within the HEROIN and METHADONE groups even when 'true' scores are used.
- (5) Factors such as age, SIMD and others might be contributing to this heterogeneity.

A second set of confirmatory factor analyses could then be used to assess the heterogeneity in methadone treatment response when 'true' scores are used.

Improved and alternative sampling techniques

In order to ensure that the results of studies are generalisable, it will be important for future studies to be conducted using community samples and across cultures. It will also be important to utilise both developmental and genetically sensitive designs and sampling techniques. Whilst much more expensive to conduct, longitudinal studies clearly provide the strongest developmental design and should be implemented if at all possible. Genetically sensitive designs should also be considered and future studies should seek to include unaffected siblings and parents in samples.

Attempting to objectively quantify and qualify drug and alcohol use by serum and hair analysis should be further explored. Other methodological issues to be considered in future studies include:

- (a) To narrow the age, SIMD and drug history and dosage range of the recruited cohort.
- (b) Exposure to adulterants could be eliminated by recruiting individuals who are prescribed diamorphine (heroin).
- (c) Impact of the heterogeneous populations with different drug and alcohol histories (e.g. injecting behaviour) could be eliminated by using the same cohort throughout all stages of neuropsychological testing including the final stage when the same cohort are abstinent from any medication or other opioids.
- (d) Understand further the biological relationship between dependence and neuropsychological constructs used.

Issues of specificity

Whilst the current analyses have taken into account the impact of coexisting polysubstance use, dysthymia, personality traits and the effects of adulterants on neuropsychological functions, further studies are required to describe the impact of

these other disorders on neuropsychological performance both in the presence and absence of coexisting opioid dependence.

Whilst many other disorders have been associated with various deficits in neuropsychological functioning, few studies have looked at the issue of specificity i.e. which aspects of neuropsychological functioning are specific to a particular disorder and which are more general markers of psychopathology, developmental delay or vulnerability to initiation of drug use, susceptibility to dependence and ability to remain abstinent and stable on methadone treatment? Particular disorders of relevance to the current discussion include, but are not limited to, anorexia, Aspergers syndrome, ADHD, pathological gambling, OCD and other compulsive disorders, depression, schizophrenia and bipolar disorder. An alternative approach is to investigate neuropsychological functioning in an epidemiological sample and to then map poor neuropsychological function (e.g. the bottom 10%) forwards onto psychopathology and impairment. Another approach is to profile all treatment seeking individuals at a neuropsychological level and follow up their outcomes.

The use of a broader range of neuropsychological tasks

Whilst the battery of tasks used in this study covered a broader range of neuropsychological functions than those used in most other similar studies. It also included both control tasks and included more than one task to address each area of functioning. It is still the case that these did not cover all of the potential neuropsychological associations with chronic opioid use. Of particular interest would be measures of reaction time such as Continuous Reaction Time (CRT) (**Bruhn, 1971**) and Serial Reaction Time (SRTT) (**Cleeremans, 1991**), verbal memory tasks such as Auditory Verbal Learning Test (AVLT) (**Van der Elst *et al.*, 2005**) and Digit Forward and Digits Backward Test (DFDBT) (**Lezak, 1994**), and verbal fluency tasks such as the Verbal Fluency Test (VFT) (**Benton, 1978**) and Controlled Oral Word Association Test (COWAT) (**Loonstra *et al.*, 2001**).

Wherever possible studies should use tasks, like those in the CANTAB, that are rooted in laboratory neuroscience and for which aspects of the neuroanatomical and pathophysiological substrates are understood. This could be improved by making neuropsychological tasks more ecologically valid (**Verdejo-Garcia *et al.*, 2007a**).

Measurement across the various levels of analysis

Future studies should include measures across the various levels of analysis. Thus it will be important to integrate genetic, environmental, imaging and electrophysiological measures into neuropsychopharmacological study designs and vice versa.

Such studies are essential if we are to directly test proposed causal models and develop new ones. The neuropsychological deficits described here are generally thought of as endophenotypes, intermediate factors that bridge the gaps between genetic and environmental causative agents and their effects on pathophysiology and brain structure and functioning on the one hand, and the behavioural phenotype on the other. Whilst indirect evidence can sometimes be used to hypothesise the bridges between these different levels of analysis, only direct evidence from well designed studies can really provide an adequate level of proof. Clearly such studies will be costly and will require close collaboration between groups with complementary skills, however, the payoff from a comprehensive, well designed and well powered study would be immense.

The use of other opioid medications

Whilst methadone is both the best understood and most commonly used medication to treat opioid dependence, there are other treatments available. These include licensed medications such as buprenorphine (Subutex®) and buprenorphine/naloxone combination (Suboxone®), and unlicensed but relatively well established medications such as diamorphine, and dihydrocodeine. Each of these has different mechanisms of action and therefore may also impact differently on neuropsychological functioning. Further studies are required to understand how each of these drugs impact on

symptoms and neuropsychology. Clearly the hope for the future is that we can move to a situation whereby once one understands an individual's neuropsychological profile, it will be possible to predict which medication, combination of medications and appropriate treatment package will be the most likely to improve performance and symptoms and reduce impairment. It will also be informative to measure the associations between the clinical and neuropsychological impact of non-pharmacological treatments, including cognitive behavioural, relapse prevention techniques and motivational enhancement therapies together with the effects of social stability.

The use of broader measures of clinical outcome

Lastly it will important that future studies include a broad range of outcome measures that access multiple viewpoints by either using cross linkage electronic databases, both subjective (e.g. rating scales) and objective (e.g. academic productivity, neuropsychological testing and functional imaging), and measures of symptoms, impairments and quality of life. By doing so we may be able to develop a better understanding of the impact of chronic opioid use, which would not only help us understand their mechanisms of action and potential benefits, but also their limitations and potential adverse effects in order that, in the future, treatments can be targeted more efficiently, effectively and safely. It will also allow new biopsychosocial treatments to be developed which allows personalised care planning to occur (DH, 2009).

Such future studies have the potential to further improve our understanding of the causes and impact of chronic opioid use and aid in improving our management of this chronic and relapsing condition that currently blights the lives of many individuals as well as those of their families and communities.

Suggested future research projects

(1) Both the systematic review and cohort study identified neuropsychological impairment possibly due to 'core' addiction phenotype and/or chronic use of opioids. One way to differentiate between these two is to study a population born from opioid using pregnant mothers. Previous studies suggest that exposure to opioids in utero adversely affect neurodevelopment including decision-making (**Ornoy, 2002; Prandi *et al*, 2004; Bunikowski, 1998**). However, the nature and the magnitude of this effect remain unknown. Some of the possible ways in which decision making may be affected by opioid exposure, as suggested by these studies, are: less adaptive decision-making with impaired option selection; decreased use of previously learnt information; impaired group and social decision-making; impulsive decision making and impaired perception of relevant stimuli; inability to sustain attention; and increased in risk taking and greater reward-weighted decision-making (**Rosen, 1982; Ornoy, 1992; Guo *et al*., 2002; Hunt *et al*., 2008; Suess *et al*.,1997**).

This longitudinal study will follow up children with maternal methadone use during pregnancy; children with maternal methadone and or other drug use during pregnancy; children born to mothers with previous history of drug use but no use during pregnancy and deprivation matched children with no known maternal drug history. They will monitor the neurodevelopmental and neuropsychological progression through data linked access to school, health and other records and also utilising successive neuropsychological assessments throughout the childhood and adolescence period.

(2) The consequences of chronic opioid use in old age take a greater toll than in younger adults (**Ersche & Nutt, 2009**). With increasing age, older people metabolise the opioids slower, which may prolong or intensify the effects of the drug. Interactions between illicit substances and prescribed medication are more common in the older generation than in younger people (**Rosenberg, 1995**). Moreover, the social situation of long-term substance users is often much more unstable than in young substance users due to long-term unemployment, depleted financial

resources, lack of family support, isolation and social stigma (**Patterson & Jeste, 1999**). Older substance users are particularly vulnerable and accelerated cognitive decline further worsens their already poor state of psychosocial functioning (**Roe et al., 2010; Deakin et al., 2004**). The study has identified neuropsychological sequelae as a result of chronic opioid use in a population aged between 18 and 40 years. A similar ambispective cohort designed study will need to be replicated within the 40 and 60 year range in order to determine if similar or different impairments in cognitive impulsivity and memory are present.

(3) The neuropsychological impairment identified as putative markers of chronic heroin use need to be further explored by comparing these results with that of other specific opioids which either present as agonist (e.g. morphine and methadone) or partial agonists (e.g. buprenorphine). An ambispective multiphasic cohort designed study will be planned. The cohorts will be tested during induction to these opioids and then subsequently followed up 3, 6 and 12 months following stabilisation. If possible the same cohort will be tested again when such opioids have been stopped as part of the treatment plan and again retested 6, 12 and 18 months during this period of abstinence.

(4) It has been proposed that a progressive dysregulation of reward function could explain key features of the human addiction syndrome (**Redish et al., 2004; Redish et al., 2008**). One popular interpretation is that repeated use of addictive substances 'hijacks' the normal cognitive -neural systems for learning about rewards and punishments, such that substance-related stimuli become overvalued and non-substance stimuli become correspondingly undervalued. This work requires measurement of fast time scale ('phasic') neurophysiological signals reflecting learning the salience of changing predictors of rewards in the environment (**Hyman, 2007**).

It has also been suggested that opioid dependence is associated with other longstanding neurobiological changes (**Martin et al., 2007**). For example, grey matter

reductions in prefrontal, insular and temporal cortices in patients on methadone maintenance have been reported (**Lyoo *et al.*, 2006**). However, the effects of opioid dose and duration on brain structure was not specifically explored (**Martin *et al.*, 2007**) and the putative mechanisms of atrophic change remain unclear in the field of opioid dependence. Abnormalities of white matter tracts occur more commonly (**Lyoo *et al.*, 2004**) but have been little investigated. Therefore, in addition to fMRI, the use of diffusion tensor imaging (DTI) in conjunction with stereotactic tractography that investigates white matter tracts, and optimised voxel based morphometry using T1 imaging, will assist in studying the effects of opioids on hypothesised abnormal white and grey matter structure in patients exposed to chronic opioids – for example those on methadone maintenance. Structural and functional brain abnormalities are important to identify, as these may help to explain emerging evidence for neurophysiological abnormalities. Importantly, if group differences are identified, the neuroimaging data will be explored for correlations with opioid dosing and duration of use.

In this study, we propose to use an ambispective two phase cohort design to conduct neuropsychological and neuroimaging tests in chronically opioid-exposed subjects prescribed methadone and buprenorphine matched with equal numbers of healthy non-substance using controls.

Neuropsychological profiling of a male chronic opioid using and/or dependent individual described as three case scenarios

Case 1: A 26 year old male unemployed chronic heroin user who lived in his own accommodation in Fife between 2007 and 2009 consented to participate in this study. He had 10.75 years of education and a pre-morbid IQ of 106.12. His daily intake of opioids was 184.52 mg morphine equivalent daily and presented with an ICD-10 diagnosis of opioid and nicotine dependence. He presented with a subjective history of 6 years of regular and daily heroin use and 14 years of infrequent use of benzodiazepine, cocaine, cannabis and/or alcohol. He has never been treated in the past with methadone or had been using methadone and other opioids illicitly. He had no history of head injury, non-fatal overdoses, severe and/or acute psychiatric and medical problems or was prescribed psychotropic drugs.

During the period of drug experimentation he was liable to make risky decisions even though the quality of these decisions was not evidently poor. He was keen to act quickly on his decisions. Strategic planning deteriorated as he continued with his chronic heroin use compounded by long term visuo-spatial memory problems. After three weeks of initiating methadone his motor impulsivity and visuo-spatial memory improved. There were no problems with cognitive flexibility.

Case 2: A 27 year old male unemployed chronic methadone user who lived in his own accommodation in Fife between 2007 and 2009 consented to participate in this study. He had 10.58 years of education and a pre-morbid IQ of 108.86. His daily intake of opioids was 147.41 mg morphine equivalent daily and presented with an ICD-10 diagnosis of opioid and nicotine dependence. He presented with a subjective history of 9 years of regular and daily heroin use and 15 years of infrequent use of benzodiazepine, cocaine, cannabis and/or alcohol. He was prescribed methadone for treatment of his opioid dependence with objective evidence that he had not relapsed into illicit regular heroin or other drug use during the 6-12 month period in

treatment. He had no history of head injury, non- fatal overdoses, severe and/or acute psychiatric and medical problems or was prescribed other psychotropic drugs. During this treatment period of methadone stabilisation, he exhibited poor attention taking longer period of time to make a decision in the context of poor strategic planning and associated visuo-spatial memory problems. There were no problems with cognitive flexibility and set shifting. Length of time stable on the methadone prescribed did not help change this neuropsychological profile.

Case 3: A 34 year old male unemployed chronic opioid user who lived in his own accommodation in Fife or Tayside between 2007 and 2009 consented to participate in this study. He had 11.18 years of education and a pre-morbid IQ of 115.86. His daily intake of opioids was 59.11 mg morphine equivalent daily and did not present with an ICD-10 diagnosis of opioid and nicotine dependence. He presented with a subjective history of 5 years of regular and daily opioid use prescribed for persistent and chronic non- malignant pain of either neuropathic and/or muscular origin. He subjectively described an 18 year history of infrequent use of cannabis and/or alcohol. He had no history of head injury, non- fatal overdoses, severe and/or acute psychiatric and medical problems or was prescribed other psychotropic drugs. During the study period, he exhibited a trend towards poor strategic planning and associated visuo-spatial memory problems but did not reach significance. There were no problems with risk taking, motor impulsivity, cognitive flexibility or visuo-spatial memory.

Chapter 8: References

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